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BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN*

Observations in Nine Cases

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THE unprecedented cures of subacute bacterial endocarditis with penicillin have stimulated fresh interest in this heretofore fatal disease. During the last two years 9 patients have been treated and followed at the Lahey Clinic. The abstracts of these cases are presented for several reasons: unusual organisms were encountered in 2, surgery was instrumental in curing 1, and 1 represented the bacteria-free stage of bacterial endocarditis. The need for individualization of treatment is demonstrated, and several suggestions are made for improving present-day results.

CASE 1. A 59-year-old clerk was admitted to the hospital on January 1, 1946. He complained of weakness and substernal discomfort of 2 years' duration and a loss of 16 pounds in weight during the previous 2 months. For 6 months occasional temperature elevations had occurred. There was no history of rheumatic fever or syphilis.

Physical examination showed a pale and sickly patient with moderate pitting edema of the ankles. Slight exertion caused dyspnea. A to-and-fro murmur, loudest at the aortic area, and accentuation of the pulmonic second sound were detected. The cardiac apex was in the anterior axillary line in the sixth intercostal space. The blood pressure was 170/40 to 0, and the pulse was of water-hammer type. Other findings were basal pulmonary rales, petechiae, clubbing of the fingers, splenomegaly and tremor of the head and hands. The patient was given digitalis and a salt-free diet and kept in bed. There was no fever until the 8th day, when the temperature rose to 101°F.

Streptococcus inulinaceous was isolated from the blood. There was a mild hypochromic anemia with a normal number of leukocytes, 47 per cent of which were young forms. Blood Hinton, Kahn and Wassermann tests were negative. Urinalyses showed no abnormal findings. The blood nonprotein nitrogen was 33.8 mg. per 100 cc. Roentgenograms showed enlargement of the heart in all dimensions, congestion of the lungs and no dental infection. Electrocardiograms revealed a sinus rhythm, left-axis deviation, and occasional extrasystoles.

Figure 1 illustrates the penicillin and sulfadiazine blood levels and the results of blood cultures and penicillin sensitivity tests correlated with the temperature chart. The response to penicillin was dramatic. The temperature rapidly returned to normal, and the blood cultures became sterile. Congestive heart failure progressed, however, in spite of digitalization, avoidance of sodium, an acid-ash diet and mercurial diuretics. The patient left the hospital on the 40th day to convalesce nearer home, and 10 days later died from heart failure. Autopsy was not performed.

The value of determining both the penicillin sensitivity of the organism and the penicillin blood levels was confirmed in this case. Had the usual arbitrary doses been used without knowledge of these two determinations, insufficient penicillin would have been administered. Intramuscular administration resulted in a rapid decrease of penicillin in the blood — from 5 units per cubic centimeter an hour after injection to 0.65 units three hours later. Constant intravenous administration gives constant blood levels[1] and appears to be more efficient.

Streptococcus inulinaceous, a variety of *Str. bovis*, is rarely reported in subacute bacterial endocarditis. Its true incidence in this disease cannot be determined, since bacteriologic studies are not usually made to identify individual members of the *Str. viridans* group. The strain isolated from this case proved to have a moderately high penicillin resistance.

With three negative blood cultures before discharge, presumably the infection was eradicated, but final conclusions regarding cure are not justified, since death from heart failure prevented a satisfactory period of observation. The rapid progression of heart failure after the institution of penicillin therapy in a patient digitalized and resting in bed, when previously he had not been receiving digitalis and had been moderately active, raises the question of the possible toxicity of penicillin for the myocardium. Electrocardiograms, however, failed to show any significant changes during treatment. Another possibility is that valvular changes from healing processes increased myocardial strain.

CASE 2. A 34-year-old housewife and secretary entered the hospital on September 1, 1944, with fever and malaise. There was no history of rheumatic fever. The illness had begun 16 months previously with a temperature of 104°F. and generalized aching. Petechiae and a loud apical systolic murmur were found, but repeated blood cultures were sterile. An

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intradermal test for undulant fever showed whealing, whereas agglutination tests for brucellosis were negative. There was no history of drinking of raw milk in recent years, and neighborhood herds of cows tested by the Vermont State Health Department were found free of Bang's disease. The blood sedimentation rate was 93 mm. in 1 hour. A roentgenogram showed slight cardiac enlargement. A diagnosis of subacute bacterial endocarditis due to *Brucella abortus* was made, and the patient was given blood transfusions and injections of brucellergin. Only temporary improvement occurred, and sulfadiazine and arsenicals were unsuccessfully used. Intravenous injections of typhoid vaccine failed to cause a rise in temperature. Repeated blood cultures were sterile, and the sedimentation rate varied between 40 and 100 mm. in 1 hour. Just before admission the patient had been given a total of 2,000,000 units of penicillin intramuscularly at intervals of 3 hours for 7 days.

On admission the patient did not appear ill, but she had lost 19 pounds. A loud apical systolic murmur was noted. There was no enlargement of the spleen or clubbing of the fingers. A gram-negative bacillus identified as *Br. abortus* was grown in four cultures, hemolytic *Staphylococcus aureus* on four, a diphtheroid on one and hemolytic and nonhemolytic staphylococci and gram-positive bacilli on one; six cultures were sterile. The staphylococci were all coagulase negative and may therefore have been contaminants. Agglutination tests with the patient's serum and stock vaccines of Brucella organisms failed to show agglutination. The patient's serum agglutinated the isolated gram-negative bacilli in a titer of 1:5120. Urinalyses showed pyuria, and hemograms, a mild hypochromic anemia. A blood Hinton test was negative.

The following treatment failed to sterilize the blood stream: 400,000 units of penicillin intravenously daily for 19 days; sulfadiazine, which effected a blood level of 6 to 17.5 mg. per 100 cc. for 10 days; and sulfamerazine with a blood level of 11.2 to 15.8 mg. per 100 cc. for 12 days. The patient was discharged unimproved.

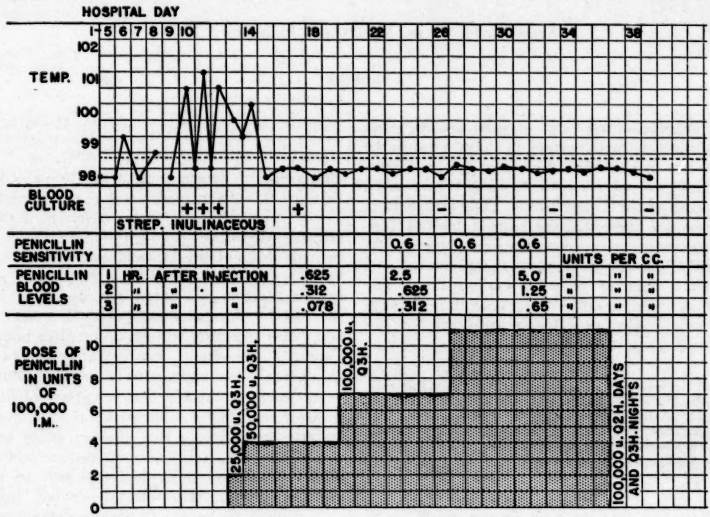

FIGURE 1. *Summary of Data in Case 1.*

Few cases of bacterial endocarditis due to *Br. abortus* have been reported, and no satisfactory treatment has evolved. Trial with modern antibacterial substances failed in this case. Streptomycin appears to be of value in some cases of brucellosis,[2] but its final evaluation in this infection awaits future study; the drug was not available for use in this case.

No explanation is apparent for the isolation of five different bacterial species from the patient's blood. Mixed infection is not usually encountered in bacterial endocarditis, and the question arises whether brucellosis predisposes to such a condition.

CASE 3. A 21-year-old housewife was first seen on July 25, 1944, because of dysuria and urinary frequency of 3 days' duration. A similar episode had occurred several months previously, and had responded to sulfonamide therapy. A cardiac murmur had been known to have been present since early childhood.

Physical examination disclosed a machine-like murmur and thrill over the pulmonic-valve area and cardiac enlargement to the left. The blood pressure was 120/40. Roentgenologic study revealed fullness of the left border of the heart in the region of the pulmonary conus. The transcardiac diameter was 13 cm., and the transthoracic 24.4 cm. The urine contained numerous pus cells, and a urogram showed a double ureter on the right. The urinary infection responded to sulfathiazole and subsided uneventfully. The patient was advised to have a right ureterectomy and ligation of the ductus arteriosus, but refused operation.

She remained well until 10 months later, when there developed fever, headache, arthralgia and myalgia, which did not respond satisfactorily to sulfadiazine administration at home, and on May 28, 1945, she was admitted to the hospital. In addition to the previous findings, she had a temperature of 100°F., herpes labialis and marked pallor. The blood pressure was 130/20. The blood sedimentation rate, previously normal, was 43 mm. in 1 hour. Three blood cultures grew *Str. viridans*; one showed 28 colonies per cubic centimeter of blood. The circulation time was 23 seconds with Decholin and 8 seconds with ether. The venous pressure was equivalent to 80 mm. of water. An electrocardiogram showed a diphasic T wave in Lead 1 and a prominent Q wave in Lead 3.

The patient was given 200,000 units of penicillin intramuscularly daily for 7 days, and the blood stream became sterile. Dr. Ralph Adams then ligated and resected the patent ductus arteriosus. Following operation, 40,000 units of penicillin was given intramuscularly every 3 hours for 3 weeks, and blood cultures remained sterile.

Shortly before discharge, roentgenographic studies showed the pulmonary conus to be less prominent, and the aortic arch to be slightly wider. An electrocardiogram revealed prominent Q waves in Leads 2 and 3 and increased voltage of the T waves in all leads. A faint systolic murmur persisted at the pulmonic area. The patient left the hospital on June 30.

A month later she was admitted to an out-of-town hospital because a blood culture had been found to contain a few colonies of *Str. viridans*, and although subsequent cultures were negative, a total of 4,000,000 units of penicillin was given. A letter from her physician reported her to be well and free of any signs of infection 22 months later.

It is not unusual for patients with a patent ductus arteriosus to develop blood-stream infection. Abbott[3] found such a complication in 21 of 92 patients with this congenital heart lesion. Only recently has the combined use of surgical ligation and penicillin changed the fatal outcome. In suitable patients the best time to carry out operation is before infection has occurred, both to prevent subsequent endarteritis or endocarditis and to protect the heart from further strain. The largest series of cases is that of Gross,[4] who reported successful division of the ductus arteriosus in 14 patients, 2 of whom had a superimposed *Str. viridans* endocarditis.

Case 4. A 45-year-old silver-press foreman was admitted to the hospital on December 12, 1944. There was no history of rheumatic fever. Five months previously anorexia, weight loss, fever, chills and soreness of the fingertips had developed. Pneumonia was suspected, and treatment with sulfathiazole carried out. The patient improved, but the temperature continued to be elevated, spiking to 106°F. Numerous blood cultures and one bone-marrow culture were sterile. He was given penicillin in doses unknown to us for 18 days and is said to have shown improvement. No further therapy was used for the next 3 months.

On admission the patient appeared to be extremely ill. He had lost 20 pounds in weight. A *café au lait* color was noted. There was marked dental sepsis. A Grade III diastolic murmur heard in the left parasternal line was loudest in the 3rd costal interspace. Rales were detected in the lung bases. The fingers were clubbed, and the edge of the spleen extended 5 cm. below the costal margin, but there were no petechiae.

Twelve blood cultures were sterile. A bone-marrow biopsy grew a nonhemolytic pleomorphic anaerobic streptococcus. Agglutination tests for undulant and typhoid fever gave negative results. Examination of the blood showed a mild hypochromic anemia, a normal number of leukocytes and a slight increase in the percentage of young cells. Urinalysis and a blood Hinton test were negative. X-ray examination disclosed that the heart was enlarged in all diameters, and the lungs were clear.

For 6 days the patient was given sulfadiazine to maintain a blood level of 12.8 to 14.8 mg. per 100 cc., with dicoumarol to reduce the prothrombin time of the blood to 48 to 77 per cent of normal. Three transfusions were given, and for the last 6 days of his life he received 400,000 units of penicillin daily by constant intravenous drip.

The fever remained intermittent, with peaks to 101°F. The murmur did not change until the day before death, when it was notably louder. The patient's condition continued to deteriorate uninfluenced by therapy, and he died 37 days after admission.

Autopsy. Post-mortem examination showed moderately sclerotic aortic cusps. The posterior cusp was torn at its left attachment to the aorta. Microscopically, there was fibrin at the tip of one of these cusps, and between the meshes of fibrin were leukocytes and a homogenous red substance. A Gram-Weigert stain was made, but no bacteria were identified. Near the base of one cusp there was an area about half the size of a low-power field filled with congested blood vessels and rather heavily infiltrated by polymorphonuclear leukocytes and lymphocytes. In the neighboring endocardium and subendocardium of the heart wall there was diffuse infiltration with polymorphonuclear leukocytes — in some places to the extent of forming small true abscesses. Other significant autopsy findings were congestive heart failure, extramedullary hematopoiesis and focal embolic glomerulonephritis.

This case represents the bacteria-free stage of bacterial endocarditis. Numerous blood cultures on special mediums failed to grow organisms, and special studies at autopsy failed to demonstrate bacteria. The significance of organisms isolated from the bone marrow is doubtful, for bacteria may lie dormant in the marrow for long periods with no relation to blood-stream infection.[5] The fever in bacteria-free cases may be due to multiple small emboli similar to those found at autopsy in the kidney. Such a case is predestined to therapeutic failure with antibacterial substances, since bacteria are no longer responsible for the illness. It is possible that a prolonged period of anticoagulant therapy in these cases would prevent thrombi from forming on the heart valves and further embolization until healing had occurred.

Case 5. A 42-year-old teacher entered the hospital on June 16, 1944, for decision regarding the need of further therapy. Two months before admission he had begun having grippe-like symptoms, elevations of temperature, occipital pains, paresthesias of the right arm and face and vomiting. He was hospitalized elsewhere, and blood cultures were taken. The thirteenth grew *Str. viridans*. One million one hundred thousand units of penicillin was given by constant intravenous drip from May 27 to June 4. Two days later the fever recurred, and urticaria appeared. Penicillin was again started, and from June 7 to June 16, a total of 28,000 units was given intramuscularly every 3 hours. Both the fever and the urticaria disappeared shortly after this second course had been instituted.

On admission the patient was asymptomatic. Early clubbing of the fingers was noted. The blood pressure was 120/70. A presystolic murmur and a snapping first sound were heard at the apex of the heart. There was no splenic enlargement, petechiae, dental sepsis or joint pains. The temperature and pulse remained normal.

Six blood cultures showed no growth. Urinalysis and a blood Hinton test were negative, and a hemogram, electrocardiogram and roentgenogram of the chest were normal. The blood sedimentation rate was 54 mm. in 1 hour. No further treatment was deemed necessary.

In a follow-up letter 23 months after discharge a physician stated that the patient had remained perfectly well. There had been no sign of recurrence, but as an added precaution he had been hospitalized on three occasions at intervals of 6 months for a course of 1,000,000 units of penicillin.

It is noteworthy that the diagnosis was made early in this case. Although only moderate doses of penicillin over a relatively short time were used, the patient remained cured twenty-three months later. It is doubtful that the subsequent courses of penicillin were needed, since at no time was there any sign of recurrence. An interesting observation is the occurrence of urticaria shortly after the first course of penicillin, and its disappearance soon after institution of the second course. That the sedimentation rate of the blood does not determine cure is shown by its elevation even after cure had been established. Goerner, Geiger and Blake[6] have reported its persistent elevation in some cases for more than six weeks.

CASE 6. A 57-year-old woman entered the hospital on May 10, 1944. In childhood she had had rheumatic fever. Six months before admission there had been fleeting joint pains and a low-grade fever that did not respond to salicylate therapy. Two blood cultures grew *Str. viridans*. In spite of satisfactory concentrations of sulfadiazine in the blood, cultures remained positive, temperature elevations continued and occasional petechiae were found.

Physical examination disclosed a *café au lait* color, a rim of fine new pink skin at the nail bases, indicative of early clubbing, a systolic murmur at the apex heard only in the left lateral position, an accentuated apical first sound, carious teeth, a tender, red swelling of the left instep and tenderness of the right elbow. The patient had lost several pounds in weight but did not appear acutely ill. There was no splenic enlargement, and the lungs were clear. Roentgenograms of the chest showed no cardiac enlargement. The blood sedimentation rate was 79 mm. in 1 hour. Blood cultures grew *Str. viridans*. Urinalyses were negative, and hemograms normal.

One million units of penicillin was given by constant intravenous drip during the next 10 days, followed by 12,500 units intramuscularly every 3 hours for another 10 days. There was clinical improvement, with remission of the fever and disappearance of the joint pains. The heart murmur increased in intensity. The sedimentation rate dropped to 48 mm. in 1 hour, and the patient was discharged.

Shortly after her return home she suffered a relapse that was treated with 2,000,000 units of penicillin. A report, 24 months later, stated that she was perfectly well.

This patient was the first to be treated with penicillin at the clinic, and supplies were scarce. The successful outcome, like that in Case 5, proves that an occasional patient with bacterial endocarditis responds satisfactorily to small doses of penicillin given over a relatively short time. Nevertheless, now that penicillin is plentiful, large doses over a long period should be used to allow a good margin of safety. If relapse occurs, further treatment may be successful, as in this patient. The change in the intensity of the heart murmur under treatment suggests structural change in the valve as a result of healing of the infected cusps.

CASE 7. A 32-year-old machinist was admitted to the hospital on December 29, 1944, because of polydipsia, polyuria, fever, chills, diarrhea and malaise of 7 days' duration. In 1934 he was said to have had hematuria and similar symptoms. Blood cultures taken elsewhere were reported to have grown gram-positive staphylococci and streptococci. A total of 470,000 units of penicillin had been given intramuscularly by a physician.

Physical examination revealed no signs of bacterial endocarditis other than petechiae. A chest roentgenogram was normal. The urine contained a trace of albumin, and the sediment showed occasional red and white cells. Examination of the blood was negative, except for a white-cell count of 12,500. The blood sedimentation rate was 100 mm. in 1 hour. A blood culture taken soon after admission showed a coagulase-positive *Staph. aureus*.

The patient was given 20,000 to 30,000 units of penicillin intramuscularly every 2 hours, and 2,420,000 units was administered during the next 32 days. The temperature varied from 99 to 103.6°F., and the urine continued to show blood cells and casts. The white-cell count remained between 10,000 and 20,000. The heart sounds remained normal until January 6, when a systolic murmur and thrill were found in the aortic area, and a diastolic murmur over the entire precordium. Three days later the patient developed acute pulmonary edema, which responded to atropine. On January 20 a pericardial friction rub was heard; 2 days later he developed pulmonary edema and died.

Autopsy. The significant findings included subacute bacterial endocarditis of the aortic valve, cardiac hypertrophy and dilatation, serofibrinous pericarditis, a recent splenic infarction, acute glomerular nephritis and congestive heart failure. Microscopical examination of firm, white nodules from the aortic valve showed fibrosis, hyalinization and infiltration by leukocytes, with a predominance of polymorphonuclear cells.

The custom of calling bacterial endocarditis acute if it has been present for less than six weeks and subacute after it has persisted six weeks or longer has less significance than heretofore. In cases that would formerly have been called subacute, penicillin often arrests the illness before it has lasted six weeks, and may prolong the course of the acute type beyond this period. A better way of classifying bacterial endocarditis is by indication of the causative organism, as in pneumonia. This case exemplifies the difficulty of distinguishing acute from subacute disease, since the clinicians considered it acute whereas the pathologists thought it subacute. We have preferred to classify it as bacterial endocarditis due to *Staph. aureus*.

CASE 8. A 28-year-old housewife entered the hospital on October 10, 1945. She had had rheumatic fever in childhood and again at the age of 22. Seventeen months before admission, she had had a sore throat and cystitis, both of which had responded rapidly to sulfonamide therapy, but malaise and a low-grade fever had continued. In August there were migratory joint pains and petechiae. Repeated blood cultures were positive for *Str. viridans*. Penicillin, heparin and sulfadiazine were administered unsuccessfully, and for 10 months the patient gave herself 15,000 units of penicillin intramuscularly every 3 hours day and night. In March a sharp pain in the left lumbar region was diagnosed as renal infarction, and in May a chest pain was called pulmonary embolism. Blood cultures remained positive, but she felt well and for 2 months before admission remained afebrile. On the day before entry she experienced a severe bilateral headache with nausea and vomiting. Cerebral embolism was suspected.

Physical examination disclosed a well nourished woman whose weight had been increasing slightly and who did not appear acutely ill. Significant findings were a temperature of 101°F., cardiac enlargement, an apical systolic murmur widely transmitted, a diastolic murmur over the left 3rd and 4th costochondral junctions and *Str. viridans* on blood culture. There were no petechiae, finger clubbing or splenic enlargement. A spinal puncture demonstrated normal dynamics of the fluid, with 297 polymorphonuclear leukocytes per cubic millimeter; a culture of the fluid was sterile. The headache disappeared after this examination, and later specimens of spinal fluid showed no leukocytosis.

Urinalyses showed a trace of albumin, and hemograms, a mild hypochromic anemia; a blood Hinton test was negative. The blood sugar and nonprotein nitrogen determinations were normal.

Three hundred thousand units of penicillin was given by constant intravenous drip daily for 6 days, 200,000 units for 2 days, and 320,000 units for 2 days. A sulfadiazine blood level of 9.1 mg. per 100 cc. was maintained for 12 days. On discharge the patient was instructed to take 15,000 units of penicillin intramuscularly every 3 hours.

One week later two or three colonies of *Str. viridans* per cubic centimeter of blood were found, and an additional 25,000 units of oral penicillin every 3 hours was prescribed. A few days later the temperature rose to 100.8°F. and there were fresh petechiae, so that 1 gm. of sulfadiazine every 4 hours was added.

The patient re-entered the hospital on November 21, and was given 500,000 units of penicillin daily by constant intravenous drip for the next 5 weeks. Three blood cultures were negative before discharge on December 28. She continued to give herself 25,000 units of penicillin intramuscularly every 3 hours. Blood cultures remained sterile, but the blood sedimentation rate continued to be elevated, and a low-grade fever persisted. On July 10, 1946, when last examined, she had gained 15 pounds in weight and felt well. The blood sedimentation rate was 66 mm. in 1 hour. Approximately 100,800,000 units of penicillin had been given during the previous 19 months.

Therapy with relatively large doses of penicillin for five weeks and with moderate doses for seventeen months failed to bring about a cure, although such treatment suppressed the infection and prevented symptoms.

Why this particular infection was so refractory to penicillin has not yet been determined since the organism was not fully identified, nor was its penicillin sensitivity studied when first isolated. At present, blood cultures are negative, and these studies cannot be made. If these investigations were made routinely at the outset in every case, information would be on hand to help explain such resistant infections. Plans are being made to administer massive doses of penicillin combined with fever therapy to this patient over a prolonged period.

Case 9. A 40-year-old executive entered the hospital on February 23, 1944. He complained of lack of energy, occasional vomiting, a weight loss of 30 pounds and intermittent elevations of temperature to 101°F. during the previous 4 months.

Physical examination revealed a systolic murmur at the apex and a to-and-fro murmur at the aortic area. The blood pressure was 130/60. The temperature was 100°F. Early clubbing of the fingers was present. A blood culture grew one or two colonies of *Str. viridans* per cubic centimeter of blood. The urine showed a trace of albumin, and the sediment contained occasional casts and white cells. Examination of the blood was negative; the blood sedimentation rate was 79 mm. in 1 hour. Agglutination tests for typhoid and Brucella infections were negative. An electrocardiogram showed only left-axis deviation. X-ray studies showed prominence of the heart to the left, apical infection of several teeth and normal sinuses and lungs.

Bacterial endocarditis was diagnosed, and 12 gm. of sulfadiazine was given daily for 9 days, in combination with four bouts of artificial fever from typhoid vaccine. Three subsequent blood cultures were sterile. Tonsillectomy and extraction of the infected teeth were done, and the patient was discharged on April 8.

A blood culture taken on the day of discharge later showed five or six colonies of *Str. viridans*, and the patient was advised to take 4 gm. of sulfadiazine daily under the supervision of his physician since no penicillin was available. Two blood cultures during May were positive.

The patient was readmitted to the hospital on June 15 and given 100,000 units of penicillin intravenously daily for 10 days and 200,000 units intramuscularly for 5 days. Soon after discharge his physician gave him another 1,000,000 units intramuscularly.

He remained well. No evidence of infection was found when he was again hospitalized 5 months later for study. As an added precaution he was given 12,500 units of penicillin intramuscularly every 3 hours for 10 days. Twenty-two months after the original penicillin treatment, his condition was still satisfactory.

The rate of progression of cardiac damage is not predictable in bacterial endocarditis. In Cases 1, 4 and 7 valvular or myocardial injury rapidly led to heart failure, whereas in Case 9 no further cardiac damage was apparent even after nine months of infection.

* * *

As demonstrated in Table 1, there was bacteriologic arrest in 7 cases and persistence of infection in 2. Of the former, 4 patients are living and well twenty-four, twenty-three, twenty-two and ten months later, respectively, and 3 died with no signs of bacterial infection. Two died from congestive heart failure, and 1 from rupture of an aortic-valve cusp. In all fatal cases repeated blood cultures before death were sterile. Autopsy was performed in 2 cases, and no organisms were demonstrated. Since it has been shown that relapses usually occur within thirty days of cessation of treatment and are rare after fifty days,[7] we consider ourselves justified in regarding the surviving patients as cured. Of the bacteriologic failures, one was due to *Br. abortus*, and the other to unknown factors.

Dental sepsis was present in 3 patients. There was none in 2, and in 4 the condition of the teeth was not stated. Infected teeth have long been suspected of being a portal of infection in bacterial endocarditis. Transient bacteremia followed tooth extraction in 75 per cent of 40 persons with marked pyorrhea and in 34 per cent of 38 persons with no dental infection.[8] Also, a number of cases have been recorded in which tooth extraction seemed to cause the bacterial endocarditis.[9] On the other hand, dental sepsis has been secondary to emboli lodging in the dentine cavity,[9] so that the role of dental infection in bacterial endocarditis is difficult to evaluate.

Other portals of infection frequently mentioned are the sinuses and gastrointestinal tract. We have seen no suggestion that the genitourinary tract is also a site for the invasion of organisms in bacterial endocarditis. In 4 cases pyuria was present, and there is a patient in the hospital who had a history of pyuria for four years and developed enterococcal endocarditis following resection of a contracted bladder outlet.

The sedimentation rate of the blood was abnormally high in all cases in which it was determined. In Case 5 it was increased to 54 mm. in 1 hour a week after the administration of penicillin had been stopped and cure established. Others have found the sedimentation rate to remain elevated for

six weeks or longer after cure,[8] and hence it is of no value as a guide for treatment or cure.

Sterilization of the blood can be accomplished in the majority of patients with penicillin-sensitive organisms, but not in all. Geiger and Goerner[10] recently reported a case in which infection persisted in spite of a sensitive organism, adequate penicillin, splenectomy and extraction of infected teeth. Other causes for failure in the treatment of bacterial endocarditis are complications from emboli or from the rheumatic heart disease and 8 per cent with congenital heart lesions develop bacterial endocarditis.[11]

Bacterial invasion of the blood stream is especially likely if a patient with a heart murmur complains of malaise, anorexia, weight loss or fever and if the sedimentation rate of the blood is elevated. We have encountered no case of bacterial endocarditis — either in our series or in reviewing the recent literature — in which there was not an elevated sedimentation rate. The routine use of this test in the

TABLE 1. *Summary of Data in 9 Cases of Bacterial Endocarditis.*

CASE No.	APPROXIMATE DURATION OF DISEASE BEFORE DIAGNOSIS	ORGANISM ISOLATED	THERAPY	REMARKS
	mo.			
1	6	*Str. inulinaceous*	25,000 units of penicillin intramuscularly every 3 hr. for 1 day 50,000 units of penicillin intramuscularly every 3 hr. for 6 days 100,000 units of penicillin intramuscularly every 3 hr. for 7 days 100,000 units of penicillin intramuscularly every 2 hr. for 10 days	Patient died of heart failure; cultures negative for 3 weeks before death.
2	16	*Br. abortus*	35,000 units of penicillin intramuscularly every 3 hr. for 7 days 400,000 units of penicillin intravenously every day for 19 days Sulfadiazine blood level of 6.0–17.5 mg. per 100 cc. for 10 days Sulfamerazine blood level of 11.2–15.8 mg. per 100 cc. for 12 days	Case considered a therapeutic failure
3	½	*Str. viridans*	25,000 units of penicillin intramuscularly every 3 hr. for 7 days 40,000 units of penicillin intramuscularly every 3 hr. for 21 days Total of 4,000,000 units of penicillin 3 mo. later	Patient well 10 mo. later
4	5	None*	400,000 units of penicillin intravenously every day for 6 days Dicoumarol for 6 days Sulfadiazine blood level of 12.8–14.8 mg. per 100 cc. for 6 days	Patient died of ruptured aortic valve; blood cultures negative; no evidence of infection at autopsy.
5	2	*Str. viridans*	160,000 units of penicillin intravenously every day for 7 days 28,000 units of penicillin intramuscularly every 3 hr. for 9 days	Patient well 23 mo. later
6	6	*Str. viridans*	100,000 units of penicillin intravenously every day for 10 days 12,500 units of penicillin intramuscularly every 3 hr. for 10 days 2,000,000 units of penicillin later	Patient well 24 mo. later
7	¼	*Staph. aureus* (coagulase positive)	30,000 units of penicillin intramuscularly every 2 hr. for 4 days 20,000 units of penicillin intramuscularly every 2 hr. for 17 days 30,000 units of penicillin intramuscularly every 2 hr. for 11 days	Patient died of heart failure; blood cultures negative for 3 wk. before death.
8	7	*Str. viridans*	15,000 units of penicillin intramuscularly every 3 hr. for 10 mo. 300,000 units of penicillin intravenously every day for 6 days 200,000 units of penicillin intravenously every day for 2 days 320,000 units of penicillin intravenously every day for 2 days Sulfadiazine blood level of 9.1 mg. per 100 cc. for 12 days 15,000 units of penicillin intramuscularly every 3 hr. for 14 days 25,000 units of penicillin orally every 3 hr. for 7 days 500,000 units of penicillin intravenously every day for 35 days 25,000 units of penicillin intramuscularly every 3 hr. for 7 mo.	Blood cultures negative, but signs of infection persist
9	9	*Str. viridans*	100,000 units of penicillin intravenously every day for 10 days 25,000 units of penicillin intramuscularly every 3 hr. for 5 days 1,000,000 units of penicillin later	Patient well for 22 mo.

*Diagnosis made on basis of clinical findings.

underlying heart disease, such as congestive heart failure, rupture of valve leaflets, perforation of the heart wall with cardiac tamponade, rupture of mycotic aneurysms or coronary occlusion, and from rupture of the spleen, massive pulmonary hemorrhage, focal nephritis with uremia, toxemia, cerebral embolism, reinfection with penicillin-resistant organisms and unrelated diseases.

Early Diagnosis

Owing to delay in diagnosis the organism becomes more firmly entrenched in a network of fibrin, with extension of damage to the heart valves, increased toxemia and complications from emboli. Such delay is frequent: it is not unusual for mild symptoms to be present for months before the diagnosis is even suspected. As many as 5 per cent of patients with examination of patients with heart murmurs would be of value in selecting those needing further investigation. If patients with heart murmurs recorded their temperatures three times a day for one or two weeks whenever they noticed a change in their state of health, earlier suspicion would be aroused, leading to prompter study. A special search should be made for petechiae, Osler nodes, Janeway lesions, splinter hemorrhages beneath the nails, glossiness of the rim of the skin at the nail bases indicative of early clubbing of the fingers,[12] splenomegaly and changes in the heart murmur. The rarity of bacterial endocarditis with auricular fibrillation is often mentioned as being of diagnostic value. In 286 cases of auricular fibrillation, however, it was found in 12.5 per cent,[13] so that the

possibility of bacterial endocarditis must not be too readily dismissed because the heart is fibrillating.

Bacteriologic Considerations

Streptococci belonging to the alpha-hemolytic group cause approximately 90 per cent of cases of bacterial endocarditis. Other organisms that have been found responsible include *Neisseria sicca*, *N. catarrhalis*, *N. gonorrhoeae*, *N. intracellularis*, *N. flava*, *Diplococcus mucosus*, *D. crassus*, *Micrococcus cinerius*, *Gaffkya tetragena*, *Staph. albus*, *Staph. aureus*, Corynbacterium, *Br. suis*, *Br. abortus*, *Br. melitensis*, *Spirillum surati*, *Streptobacillus moniliformis*, *Actinomyces necrophorus*, *Bacillus döderleini*, *Haemophilus influenzae*, anaerobic hemolytic streptococci, enterococci, pneumococci and fungi such as Monilia, Erysipelothrix, Leptothrix and Histoplasma.

Str. viridans is often discussed as if it were an individual organism, but this is not so. It is a group of streptococci that produce a green pigment on blood agar, and includes *Str. salivarius*, *Str. equinus*, *Str. bovis* and its varieties and *Str. thermophilus*.[14] Enterococci, notably *Str. faecalis*, may be mistaken for one of the viridans group unless special studies are undertaken. There has recently been reported isolation from cases of bacterial endocarditis of a *Str. viridans* that differs from other members of this group and has been designated by its discoverers *Streptococcus s.b.e.*[15]

It is not possible to compare the clinical course of infection arising from each of these streptococci, since they are rarely identified or reported. That there are differences is shown by the sensitivity to penicillin of some — for example, *Str. salivarius* — and the resistance of others, notably *Str. faecalis* and *Str. inulinaceous* (as in Case 1). With *Str. s.b.e.*, the outlook is grave.[15] The origin of the infection may be suggested by full identification, for some species inhabit the mouth, and some the intestinal tract, and others occur in animals or in milk products.

In obtaining blood for culture, at least 20 cc. should be withdrawn, preferably following a chill when the fever is mounting. Pour plates are usually made with 0.5 cc., 1 cc. and 3 cc. of blood, and the rest is divided between two flasks, each containing at least 75 cc. of broth. Enriched mediums, such as hormone broth, heart-brain broth and tryptose-phosphate broth, are preferable since fastidious organisms, as well as others, will grow in them. Growth may be delayed, so that cultures should be incubated for at least ten days before being discarded. Repeated cultures are often necessary before the organism is isolated, for the bacteria may be present only intermittently in the blood stream. Para-aminobenzoic acid to neutralize sulfonamides and clarase to neutralize penicillin are sometimes added to the culture mediums, but in most cases the diluting effect of relatively large amounts of medium is sufficient. If unusual infections are to be recognized, special bacteriologic examinations are necessary. In obscure cases, anaerobic cultural methods and special mediums, such as Sabouraud's medium, are required. Libman[16] believes that positive cultures can be obtained in 84 to 95 per cent of cases, and in 1912 demonstrated organisms in the blood stream in 73 of 75 patients with bacterial endocarditis.

Treatment

Few investigators agree on optimal methods of treatment with penicillin. Differences of opinion exist regarding proper dosage, manner of administration, duration of therapy and use of anticoagulants, but almost all agree that the dose should be large and its administration prolonged. Some workers recommend an arbitrary dose of 500,000 units daily for five weeks.[7, 17] Others individualize therapy, giving sufficient penicillin to raise the blood level five to ten times higher than that needed to inhibit growth of the organism.[1, 18] The latter method is preferable, since organisms vary in their sensitivity to penicillin, and different blood levels are obtained from given amounts of penicillin. It may be necessary to give as much as 5,000,000 units daily, as in a patient now under treatment, to obtain effective concentrations in the blood. Increased penicillin resistance of the organism, although rare,[19] may occur and remain undetected unless repeated sensitivity tests are done.

Administration by constant intravenous drip is generally considered superior to other methods, since higher and more constant blood levels are obtained.[1] Intermittent intramuscular injection is frequently employed. There does not appear to be any significant difference in the percentage of cures by either method if sufficient penicillin is used.

Anticoagulant therapy is not generally used in conjunction with penicillin, since complications are frequent and the end results do not appear to be improved. For patients who do not respond to penicillin, however, it may have a place. Loewe[1] reported 2 cases and mentioned 5 others in which the combined treatment was required to achieve cure.

Bacteriophage was found by MacNeal[20] to contribute to the cure of a patient with enterococcal endocarditis. In view of the poor prognosis in this type of infection, further trials with bacteriophage are warranted. Surgery has become increasingly important in treating bacterial endocarditis not only for eliminating foci of infection but also for correcting congenital cardiac anomalies. To our knowledge, no one has reported the use of artificial fever as an adjunct to penicillin therapy of bacterial endocarditis. Its possible value is suggested by the improvement in results with the sulfonamides when fever therapy was added.[18]

Congestive heart failure may occur during the treatment of bacterial endocarditis, and measures

to forestall this complication should be instituted. Frequently, the patient should be digitalized, activity markedly restricted, and sodium prohibited. Five per cent glucose in distilled water, rather than physiologic saline solution, should be used for the intravenous administration of penicillin. The amount of sodium in sodium penicillin need not be considered, for in 1,000,000 units there is approximately 167 mg. of the sodium ion, equivalent to the amount in about 20 cc. of physiologic saline solution.[21]

Summary

Nine cases of bacterial endocarditis are reported in which penicillin failed to sterilize the blood stream in only 2.

Earlier diagnosis would be possible if the presence of bacterial infection were questioned in all patients with heart murmurs, if such patients were instructed to record their temperatures whenever a change in health occurred and if the blood sedimentation rate were determined routinely at examinations. A plea is made for more detailed bacteriologic study of causative organisms, and especially for the identification of alpha-hemolytic streptococci.

Treatment may be carried out with arbitrary doses of penicillin, but basing doses on penicillin sensitivity studies and determinations of blood levels ensures the administration of adequate amounts. Five weeks of therapy is generally considered satisfactory. Therapeutic failure is more frequently the result of complications from the underlying heart disease than of the infection; therefore, the importance of early diagnosis, before complications arise, is emphasized.

References

1. Loewe, L. Combined use of anti-infectives and anticoagulants in treatment of subacute bacterial endocarditis. *Bull. New York Acad. Med.* **21**:59-86, 1945.
2. Herrell, W. E., and Nichols, D. R. Clinical use of streptomycin: study of forty-five cases. *Proc. Staff. Meet., Mayo Clin.* **20**:449-462, 1945.
3. Abbott, M. E. *Atlas of Congenital Cardiac Disease.* 62 pp. New York: American Heart Association, 1936.
4. Gross, R. E. Complete surgical division of patent ductus arteriosus: report of 14 successful cases. *Surg., Gynec. & Obst.* **78**:36-43, 1944.
5. Barbagallo, G. La sterno-medullo-cultura nelle malattie infettive. *Policlinico (sez. med.)* **45**:230-243, 1938.
6. Goerner, J. R., Geiger, A. J., and Blake, F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents. *Ann. Int. Med.* **23**:491-519, 1945.
7. Christie, R. V. Penicillin in subacute bacterial endocarditis: report to Medical Research Council on 147 patients treated in 14 centres appointed by Penicillin Clinical Trials Committee. *Brit. M. J.* **1**: 381-383, 1946.
8. Okell, C. C., and Elliott, S. D. Bacteriaemia and oral sepsis, with special reference to aetiology of subacute endocarditis. *Lancet* **2**: 869-872, 1935.
9. Barnfield, W. F. Subacute bacterial endocarditis and dental procedures. *Am. J. Orthodontics* (Oral Surg. Sect.) **31**:55-88, 1945.
10. Geiger, A. J., and Goerner, J. R. Benzyl penicillin: failure to sterilize blood in subacute bacterial endocarditis. *Yale J. Biol. & Med.* **18**: 377-380, 1946.
11. White, P. D. *Heart Disease.* Third edition. 1025 pp. New York: Macmillan Co., 1944.
12. Hurxthal, L. M. Clinical observations on sub-acute bacterial endocarditis. *Boston M. & S. J.* **197**:41-46, 1927.
13. McDonald, R. K. Coincidence of auricular fibrillation and bacterial endocarditis. *Am. Heart J.* **31**:308-313, 1946.
14. Sherman, J. M. Streptococci. *Bact. Rev.* **1**:3-97, 1937.
15. Loewe, L., Plummer, N., Niven, C. F., Jr., and Sherman, J. M. Streptococcus a.b.e. in subacute bacterial endocarditis. *J. A. M. A.* **130**:257, 1946.
16. Libman, E., and Friedberg, C. K. *Subacute Bacterial Endocarditis.* Edited by H. A. Christian. 108 pp. New York: Oxford University Press, 1941.
17. Flippin, H. F., Mayock, R. L., Murphy, F. D., and Wolferth, C. C. Penicillin in treatment of subacute bacterial endocarditis preliminary report on twenty cases treated over one year ago. *J. A. M. A.* **129**:841-843, 1945.
18. Favour, C. B., Janeway, C. A., Gibson, J. G., II, and Levine, S. A. Progress in treatment of subacute bacterial endocarditis. *New Eng. J. Med.* **234**:71-77, 1946.
19. Editorial. Dosage of penicillin. *New Eng. J. Med.* **234**:706-708, 1946.
20. MacNeal, W. J., Blevins, A., and Poindexter, C. A. Clinical arrest in enterococcal endocarditis. *Am. J. M. Sc.* **211**:40-50, 1946.
21. Gibson, A. Personal communication.

PERSISTENCE OF REMISSIONS OF THYROTOXICOSIS AFTER CESSATION OF THIOURACIL THERAPY*

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THE great effectiveness of thiouracil and related compounds in controlling thyrotoxicosis has been well established. In most cases this type of therapy can be continued for many months or years without the production of ill effects or a state of refractoriness. One cannot be certain, however, that undesirable metabolic abnormalities will not develop after long intervals of therapy. For this reason, as well as others, it is important to determine the optimal treatment necessary to produce remissions that will be sustained after cessation of thiouracil therapy. Only a few results dealing with this subject have been reported.[1–7] Approximately a year ago it was found that of 100 patients with thyrotoxicosis treated with thiouracil, 49 were in a remission for intervals of three to twenty-one months following the discontinuance of treatment.[6] These studies have been extended and are the basis of this report.

The types of cases treated, the outline of therapy and the nature of the follow-up examinations have previously been presented.[6] So far as the selection of cases for treatment without thyroidectomy is concerned, the only factor that appears to be significant is that few patients with thyroid glands more than five times the normal size were treated.

This report presents the results in all patients who had a cessation in thiouracil therapy, including the cases in which the patient stopped treatment of his own accord. Seven patients disappeared from the clinic during their second or third course of therapy and were not heard from in spite of repeated solicitations. All of these are included in the group experiencing relapses of the disease, but it is possible that some of them are now in remission. Several of the other patients, especially the ones with sustained remissions, would probably have disappeared from observation had it not been for special requests for their return.

On cessation of thiouracil therapy the patients were given a clinical examination and a test of basal metabolic rate at monthly intervals for four months, bimonthly until the end of a year and then at intervals of from three to six months.

Of the 111 patients who were treated with thiouracil or one of its derivatives and had a discontinuation of therapy, 47 have had no evidence of reappearance of thyrotoxicosis, although they have not received any treatment for intervals of from three to thirty-one months. In addition, 4 patients, after receiving a second course of thiouracil therapy, have experienced a sustained remission for intervals of from five to thirteen months. Thus, 51 of the 111 patients, or 46 per cent, appear to need no more treatment. Indeed, 44 have been free of thyrotoxicosis for more than a year after cessation of therapy, and 33 have remained well for more than eighteen months (Fig. 1). Moreover, of the patients who have been well for more than a year without treatment, only 1 has had a relapse of the thyrotoxicosis. Most of the patients who had a relapse had it within a few months: 70 per cent had it within two months, and 88 per cent within five months. One patient, however, had a relapse after having been well for thirteen months without treatment.

Many of the patients who experienced relapses were treated again with thiouracil. Of 12 who have again had a cessation of therapy 4 have had a persistent remission, but 8 have had another relapse. Four of the 8 patients, however, were treated for less than six months in the second course of therapy.

Only 4 of 21 male patients, or 18 per cent, had a sustained remission, whereas 47 of 90 female patients, or 52 per cent, remained well. Those experiencing a decrease in the size of the thyroid gland while receiving thiouracil treatment were more prone to have a sustained remission of the disease than the ones whose glands increased in size or showed no change. Patients with small goiters or slight thyrotoxicosis experienced a more persistent response than the ones with large goiters or severe thyrotoxicosis. Factors that did not seem to be of much significance in obtaining a persistent remission were the age of the patient, the duration of the disease and the nodularity of the thyroid gland. The duration of therapy was of distinct significance, but varied a great deal in different cases. In fact, none of the 3 patients treated continuously for the longest interval remained well (Fig. 2).

In a consideration of the correlation of the duration of treatment with sustained remissions of

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thyrotoxicosis that were obtained, it is to be borne in mind that the prolonged course of therapy in some cases was due to the suggestion by the clinical course of the patient that a relapse would probably result if the therapy were discontinued. The decision regarding when treatment was to be discontinued was, in part, based on the maintenance dose of thiouracil that was required.

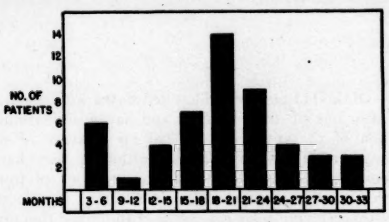

FIGURE 1. *Duration of Sustained Remissions.*
All the patients included in this chart are in a state of euthyroidism at present. Thus far, none of our patients, except one who has been free of thyrotoxicosis for a year, have had a reappearance of this disease.

Nine patients were treated with thiouracil during pregnancy for a month or longer. Three were treated for several months before fertilization, with continued therapy throughout pregnancy. The thyrotoxicosis was well controlled. No infants were found to have a goiter or a disturbance in thyroid function at birth or during the interval of more than a year that they have been followed.

Of 9 female patients with malignant exophthalmos, 5 have had a remission that has persisted after cessation of therapy. None of the 4 male patients with this disturbance, however, have remained well.

In none of the more than 300 patients that we have treated with thiouracil or one of its derivatives has carcinoma of the thyroid gland been found, although some patients have received one of these drugs most of the time for three years. Moreover, in the majority of cases treated for eight months or longer, the thyroid gland was found to have decreased in size or not to have shown any essential change.

No untoward effects, other than the types of toxic reactions that have been observed with short intervals of thiouracil therapy, have been demonstrated in the patients given this compound for a year or longer. Such complications, however, must continue to be considered.

The following brief résumés of some of the case reports are presented to indicate the nature of the problems and the results obtained.

Cases with Persistent Remissions

CASE 21. A 36-year-old Negress, during the 13 months before admission, had observed nervousness, hyperhidrosis, heat intolerance, weakness, fatigue, goiter, hyperorexia, a loss of 35 pounds in weight, palpitation, dyspnea and slight exophthalmos. Physical examination revealed a moist, hot skin, a tremor, a pulse rate of 120, slight exophthalmos, diffuse enlargement of the thyroid gland to approximately two and a half times the normal size and a loud bruit. The basal metabolic rate was above +80 per cent on two occasions, and the protein-bound iodine was 14 microgm. per 100 cc. of plasma. With no treatment other than thiouracil, the basal metabolic rate became normal within 2 months and has subsequently remained normal for 32 months, although no treatment has been given for the last 17 months. The patient regained all the weight that she lost and has felt well in every way.

CASE 31. A 32-year-old Negress stated that for 5 months before hospitalization she had been bothered by nervousness, weakness, fatigue, hyperorexia followed by anorexia, diarrhea, a loss of 50 pounds in weight, palpitation, tachycardia, dyspnea, orthopnea, edema of the legs, hyperhidrosis and heat intolerance. Physical examination disclosed congestive heart failure, with a pulse rate of 110, a warm, moist skin, a tremor, marked exophthalmos, nodular enlargement of the thyroid gland to three times the normal size and a loud bruit. The basal metabolic rate was +64 per cent, but 1 month after the beginning of thiouracil therapy it was normal. This drug was given continuously for 18 months, during the last 9 of which the patient was pregnant, giving birth to healthy twins. The dosage of thiouracil during the last 5 months of pregnancy was 0.2 gm. daily. Although therapy has been discontinued for 18 months, the patient has remained in excellent condition. She has gained a total of 85 pounds, and the thyroid gland seems to be normal in size, shape and consistence.

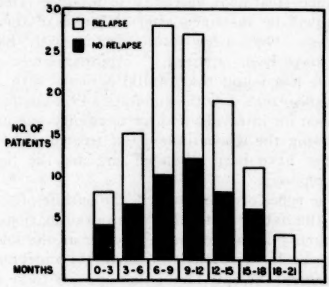

FIGURE 2. *Interval of Continuous Treatment.*
The percentage of sustained remissions does not appear to be particularly affected by the duration of therapy. In some cases, however, the duration of the therapy was governed by the response of the patients while they were receiving thiouracil.

CASE 77. A 35-year-old woman had had moderately severe thyrotoxicosis of 5 months' duration, malignant exophthalmos, diffuse enlargement of the thyroid gland to approximately one and three quarter times the normal size and elevation of the basal metabolic rate to +55 per cent. The response of the thyrotoxicosis to thiouracil was slow; no more than 0.4 gm. daily of this compound was used because of the malignant exophthalmos. In spite of this precaution, the ophthalmopathy became worse, so that treatment with desiccated thyroid was begun. Thereafter, the eyes and the thyrotoxicosis showed slow improvement. Thiouracil was given for 11 months and was then discontinued, as was the desiccated thyroid. The patient has been free of hyperthyroidism for 18 months subsequently, and during this interval she went through a normal pregnancy. The exophthalmos has improved slightly.

CASE 99. The patient was a 51-year-old unmarried woman who had moderately severe thyrotoxicosis that had begun 2 months before treatment with thiouracil. The basal metabolic rate decreased from +62 per cent to −9 per cent after treatment for 5 weeks. Therapy was continued for 11 months.

The patient has remained in excellent condition in spite of the cessation of treatment 18 months ago. The thyroid gland, which was two and a half times the normal size before treatment, is about one and three quarters times normal.

CASE 154. A 28-year-old Finnish woman had had thyrotoxicosis for 1 year. The lowest basal metabolic rate preceding treatment had been +31 per cent, and the rate became normal within 4 weeks after thiouracil therapy was started. The treatment was continued for only 6 months, but the patient has remained entirely well for 21 months subsequently. During that time she has gone through a normal pregnancy. The thyroid gland, which was estimated to be one and three quarters times the normal size before therapy, seems to be normal in every respect.

CASE 178. A 63-year-old woman with thyrotoxicosis of 3 months' duration was found to have a basal metabolic rate of +47 per cent. Within 4 months of treatment with thiouracil, the metabolic rate was normal. This therapy was given for a total of 8 months and was discontinued, but the patient has remained well for 14 months subsequently. The thyroid gland, which was about one and a third times the normal size before treatment, is normal.

Cases with Relapses

CASE 2. A 55-year-old painter had had symptoms of thyrotoxicosis for 1 year. The disease was severe and was associated with heart failure and malignant exophthalmos. The thyroid gland was about three times the normal size. The basal metabolic rate was +84 per cent. Within 4 weeks after thiouracil therapy was started, the basal metabolic rate was normal. After treatment was given for 5 months, the patient failed to return to the clinic, in spite of repeated requests. Seven months later, he returned in a condition that was almost as poor as that at the beginning of treatment. With thiouracil therapy, the basal metabolic rate became normal after 10 weeks. This course of treatment was continued for 10 months, but the patient had a relapse 1 month thereafter. A third course of thiouracil therapy was started, but the patient disappeared after it had been given for 2 months.

CASE 4. A 49-year-old female factory worker had had thyrotoxicosis for 22 years. During the early phase of the illness she had been subjected to three thyroid operations. She had taken Lugol's solution periodically for 22 years. The basal metabolic rate was +56 per cent, and the thyroid gland was about two and a half times the normal size. She showed an adequate response to thiouracil, but this therapy was given continuously for 20 months. She remained in excellent condition for 4 months after cessation of therapy but developed a relapse during the subsequent month. Potassium iodide did not cause a complete response. Thiouracil, in amounts of 0.2 gm. daily, was then given, but the patient developed agranulocytosis. Thereafter she was treated satisfactorily with radioactive iodine.

CASE 5.* A 35-year-old housewife had had mild thyrotoxicosis for 1 year. The basal metabolic rate was +45 per cent, and the thyroid gland was two and a half times the normal size. The disease was readily controlled with thiouracil, and the basal metabolic rate finally decreased to −25 per cent under a maintenance dose of 0.1 gm. every 2 days. This therapy was given for 11 months and then discontinued. The patient, however, had a relapse 6 weeks later. On reinstitution of thiouracil therapy a febrile reaction occurred; a similar reaction followed tetramethylthiourea. Potassium iodide was then given, but within 3 days a violent bullous eruption developed. This therapy was discontinued, and the patient was then treated satisfactorily with radioactive iodine.

CASE 14. A 52-year-old railroad fireman with severe thyrotoxicosis of 3 months' duration had a thyroid gland that was three times the normal size and a basal metabolic rate of +64 per cent. He showed a standard response to treatment with thiouracil; the dosage in this case was initially about 1 gm. daily, as was that in the other cases at this early stage of development of thiouracil therapy. After the patient had been treated for 4 months, the thyroid gland had increased to six times the normal size, but with 2000 r of x-ray therapy over the gland, it decreased to its original size. Thiouracil treatment was discontinued after it had been given continuously for 19 months. The patient remained in good condition for 2½ months but then had a relapse. Another remission was readily induced with 6-methylthiouracil and was maintained with potassium iodide, which was given for 4 months. Three months after cessation of this therapy, a relapse occurred. Another remission was produced within 3 weeks, 6-butylthiouracil therapy being employed. Potassium iodide was then used as the only treatment for 6 weeks. A relapse occurred 4 months after the iodide had been stopped. Radioactive iodine is now to be used.

*This case was reported by Chapman and Evans[8] in 1946 (Case 16).

Miscellaneous Cases

One patient has taken thiouracil most of the time for three years. Of her own volition, she stopped the treatment five times; on each occasion she permitted a lapse of about two months without therapy, and each time a relapse occurred within about a month. A patient who had taken thiouracil continuously for eighteen months had a relapse within a month after stopping treatment. A second course of therapy was given for nine months, consisting of thiouracil for the first two months and potassium iodide for the last seven. She has remained in excellent condition for ten months following the cessation of antithyroid treatment. Another patient† received thiouracil for eight months and had a remission that persisted for ten months after therapy had been stopped. She then had a relapse, which was treated for a month with ethyl-diiodobrassidate[9]; a remission has been present for eight months. Still another patient,† treated with thiouracil for six months, had a remission lasting six months after treatment was stopped. Although a moderately severe relapse occurred, she responded well to para-aminobenzoic acid, obtaining a remission that has lasted for eight months since the cessation of therapy. One patient who was receiving desiccated thyroid for hypometabolism at the time she developed thyrotoxicosis not only had a remission of the Graves's disease that has lasted for twenty-eight months but also again developed hypometabolism with a basal metabolic rate of −27 per cent. One patient has received tetramethylthiourea, thiouracil or propylthiouracil continuously for twenty months, because on the basis of the maintenance doses necessary, it is apparent that a relapse would soon take place if treatment were to be stopped. In another case, in which the course was similar after the administration of thiouracil continuously for a year, radioactive iodine was given, since a sustained remission did not appear promising with thiouracil therapy. In 3 similar cases the thiouracil treatment was discontinued to ascertain whether a remission would result, but in each a relapse developed within a month.

†These cases are included in the group with relapses and not in that with persistent remissions.

DISCUSSION

The results presented above indicate that thiouracil or related compounds can be used alone in the control of many cases of thyrotoxicosis. This raises the question whether thiouracil derivatives, radioactive iodine or thyroidectomy should be prescribed in most cases of thyrotoxicosis. This query can be better answered when more is learned about the possible ill effects of the newer types of treatment. On the basis of the present results, however, it appears unnecessary to perform a subtotal thyroidectomy in many cases of thyrotoxicosis. In patients with large nodular goiters and those with pronounced compression of the trachea or esophagus, thyroidectomy is indicated, but essentially all the other cases can be treated with antithyroid drugs or radioactive iodine.[8–10]

Carcinoma of the thyroid gland occurs so rarely in patients with thyrotoxicosis that the routine removal of the gland as a prophylactic measure does not seem justified.[11] There is a possibility that thyroid carcinomas are associated with radioactive iodine or thiouracil therapy, but there is no evidence of such an association.

There is also a possibility that radioactive iodine will produce damaging effects to tissues other than the thyroid gland, especially the kidneys, but no such ill effects have been demonstrated in any patient. The main handicap in depending on radioactive iodine, aside from its scarcity, is in estimating the dosage that is required. Excessive doses may produce myxedema, whereas inadequate amounts may not control the thyrotoxicosis. If the dosage of radioactive iodine is insufficient, however, additional doses can be given, or the patient can be treated with one of the thiouracils.

The newer thiouracils, especially 6-propylthiouracil and 6-cyclopropylthiouracil,[9, 12] can be used with relative safety, and it seems to be safe to dispense them widely. With this type of therapy the basal metabolic rate can be adjusted to the desired level. Moreover, with increased experience with these compounds, the frequency with which the patients must consult the physician can be greatly reduced. Whether the incidence of remissions will be the same as that with thiouracil is not known, although this appears probable. In most patients with thyrotoxicosis it appears desirable to use propylthiouracil for about nine months, or longer, before any other treatment is given. If a relapse occurs, some of the patients can be treated with radioactive iodine, and the others with additional courses of propylthiouracil.

The duration of continuous thiouracil therapy is important. It is believed that in most cases the drug should be given for nine to fifteen months. This interval is arbitrary in some cases, but in others it is indicated by the clinical course of the patient. Patients who continue to require more than 50 mg. of thiouracil daily, those with thyroid glands that enlarge even though no hypothyroidism exists, those with increasing manifestations of malignant exophthalmos and those with a loud bruit over the thyroid gland usually need to be treated for a longer interval. On the other hand, the therapy can be stopped in patients who have been in good condition for several months even with a daily dosage of thiouracil of 50 mg., the ones whose thyroid glands have decreased in size during therapy, those with no bruit over the thyroid gland and those who maintain a normal metabolic rate in spite of distressing situations. The manifestations of thyrotropic activity thus appear to be important aids in regulating the duration of therapy.

No criteria have been found that enable an accurate prediction of just which patients will develop a remission that will persist after cessation of thiouracil therapy, but a few factors are known to have some influence on the course of the disease. On the basis of the results presented above, it appears that the majority of female patients with small goiters and mild thyrotoxicosis experience a remission of the disease that persists after cessation of thiouracil therapy; the results are not so good if the thyrotoxicosis is severe, if the goiter is large or if the patient is a male. The duration of the disease preceding therapy, the age of the patient and the nodularity of the gland do not appear to influence the incidence of remissions, but as larger series of cases are analyzed and as an opportunity is afforded to control some of the variable characteristics, these factors will probably be found to affect the prognosis.

Contrary to the impression of others,[7] we do not believe that nodular goiters contraindicate prolonged thiouracil therapy. Moreover, in this clinic, pregnancy has not been a contraindication to thiouracil therapy. In fact, patients who are found to have thyrotoxicosis during pregnancy can possibly be treated more safely with propylthiouracil than with radioactive iodine or by thyroidectomy. It is essential, however, to employ the smallest amount of propylthiouracil that is necessary. For added safety, we have adopted the policy of using small doses of potassium iodide in conjunction with the propylthiouracil. It has been shown that thiouracil enters the blood of rat fetuses,[13] and that in large doses this compound produces goiter and impairment of growth of the fetuses.[13–15] Moreover, goiter has been observed at birth in a child,[16] but the dosage of thiouracil was larger than is now known to be necessary. The mother receiving thiouracil probably should not nurse her child, since the concentration of the compound in milk is high.[17]

Summary

Of 111 thyrotoxic patients who were treated with thiouracil and had a cessation of therapy, 51 are in remissions that have lasted for three to thirty-one months. Forty-four patients have been free of thyrotoxicosis for more than a year after cessation of therapy, and 33 have remained well for more than eighteen months. Of all the patients who remained well without treatment for more than a year, only 1 had a relapse. Following the cessation of treatment with thiouracil, most of the patients who had a relapse had it within a few months: 70 per cent had it within two months, and 88 per cent within five months.

Factors that tended to favor persistent remissions were as follows: female sex, small goiter and a mild degree of thyrotoxicosis. The age of the patient, the duration of the disease and the nodularity of the thyroid gland were not found to exert a significant influence, but these factors may prove important when larger series of cases are analyzed.

The good effects obtained with thiouracil encourage the frequent use of its less toxic derivative, 6-propylthiouracil, in the treatment of thyrotoxicosis. This therapy, radioactive iodine or a combination of the two appears to offer the most satisfactory method of treating the majority of patients with thyrotoxicosis, but further experiences may reveal complications from these types of treatment that are of greater magnitude than are anticipated at present. Therefore, patients treated by these newer methods must be followed carefully.

References

1. Astwood, E. B. Thiouracil treatment in hyperthyroidism. *J. Clin. Endocrinol.* 4:229-248, 1944.
2. Rose, E., and McConnell, J. Thiouracil in treatment of thyrotoxicosis: clinical experience with 37 cases. *Am. J. M. Sc.* 208:561-576, 1944.
3. Williams, R. H. Antithyroid drugs, with particular reference to thiouracil. *Arch. Int. Med.* 74:479-487, 1944.
4. Astwood, E. B. Chemotherapy of hyperthyroidism. *The Harvey Lectures.* Series XL, 1944-45. Pp. 195-235.
5. Barr, D. P., and Shorr, E. Observations on treatment of Graves' disease with thiouracil. *Ann. Int. Med.* 23:754-778, 1945.
6. Williams, R. H. Thiouracil treatment of thyrotoxicosis: results of prolonged treatment. *J. Clin. Endocrinol.* 6:1-22, 1946.
7. Beierwaltes, W. H., and Sturgis, C. C. Remissions in thyrotoxicosis after thiouracil. *J. A. M. A.* 131:735-738, 1946.
8. Chapman, E. M., and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.* 131:86-91, 1946.
9. Williams, R. H. Unpublished data.
10. Hertz, S., and Roberts, A. Radioactive iodine in study of thyroid physiology: use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.* 131:81-86, 1946.
11. Rogers, W. F., Jr., Asper, S. P., Jr., and Williams, R. H. Unpublished data.
12. Astwood, E. B., and Vander Laan, W. P. Thiouracil derivatives of greater activity for treatment of hyperthyroidism. *J. Clin. Endocrinol.* 5:424-430, 1945.
13. Williams, R. H. Further studies of absorption, distribution and elimination of thiouracil. *J. Clin. Endocrinol.* 4:385-393, 1944.
14. Hughes, A. M. Cretinism in rats induced by thiouracil. *Endocrinology* 34:69-76, 1944.
15. Goldsmith, E. D., Gordon, A. S., and Charipper, H. A. Analysis of effects of continued thiourea treatment in pregnancy and on development of offspring in rat. *Am. J. Obst. & Gynec.* 49:197-206, 1945.
16. Eaton, J. C. Treatment of thyrotoxicosis with thiouracil. *Lancet* 1:171-174, 1945.
17. Williams, R. H., Kay, G. A., and Jandorf, B. J. Thiouracil: its absorption, distribution, and excretion. *J. Clin. Investigation* 23: 613-627, 1944.

ACUTE BRUCELLOSIS AMONG LABORATORY WORKERS*

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UNDULANT fever occurs frequently among laboratory workers handling cultures of Brucella organisms.[1] This report is a summary of such infections in 17 persons engaged in investigative work with these organisms. The organization of the laboratories at Camp Detrick made it possible to gather serologic data before infection. These cases offered an unusual opportunity to observe the clinical course of this disease from the onset of illness and to submit several chemotherapeutic agents to clinical trial.

A Brucella vaccine was given to all members of the laboratory group, including the 17 who subsequently contracted brucellosis. Vaccination produced changes in the agglutination reaction and the opsonocytophagic index, and may have altered the course of illness. This report is not concerned with an evaluation of the prophylactic efficacy of the vaccine.

The patients were all previously healthy young adults who gave no history or laboratory evidence of past Brucella infection. They had been under our direct observation or cognizance for three to fourteen months, the average period being six and a half months. The diagnosis in these patients was based on the clinical course of the disease, the development of high Brucella agglutinin titers and, in most cases, the isolation of the etiologic agent from the blood. Tables 1 and 2 present many of the pertinent data.

*From the Station Hospital, Camp Detrick, Frederick, Maryland.

Clinical Aspects

Incubation Period

The data are of limited help in determining the incubation period, since all the patients were in almost daily contact with the infecting organism for three to thirteen months before they became ill. The incubation period was known to have been at least four weeks in 1 case, since there had been no opportunity for exposure for that length of time immediately preceding the onset of the illness.

Symptoms

The interval between the appearance of the first prodromal symptoms and the time when illness was well established and incapacitating was less than twenty-four hours in 4 patients. The interval was less than seven days in all patients except one, whose symptoms increased slowly over a thirty-day period.

The clinical picture presented by nearly all patients on admission to the hospital was that of an acute and moderately severe febrile illness. The symptoms were such as are frequently associated with many other acute infectious diseases and were in no way pathognomonic. Chief among them was fatigue, which was experienced to a moderate or marked degree by all patients in the series. Aches and pains in the muscles or joints, or both, occurred in 15 patients; the pains, which were usually dull, intermittent, multiple and not clearly localized, often recurred far into the period of convalescence.

Headache was present during the acute phase of illness in a majority of cases and was the most prominent symptom in a few. Approximately half the patients experienced one or several shaking chills. Other symptoms included mild nonproductive cough, moderate nausea, occasional vomiting and photophobia. Diarrhea was present in 4 patients, being moderately severe in two.

TABLE 1. *Summary of Clinical and Laboratory Data in 9 Patients with Acute Brucellosis.*

Case No.	Age	Sex	Agglutinin Titer	Highest Agglutinin Titer		Opsonocytophagic Index				Brucellergen Skin Test		
			Before Immunization	After Immunization	After Infection	Before Immunization	Highest Reading After Immunization	Lowest Subsequent Reading Before Onset of Illness	Highest Reading After Infection	Before Immunization	After Immunization but Before Illness	Activation After Infection
1	yr. 26	F	Negative	1:200	1:6400	Negative	Marked	Slight	Moderate	Negative	—	Yes
2	24	M	Negative	Negative	1:6400	Negative	Negative	Negative	Slight	Negative	Negative	No
3	21	F	Negative	—	1:3200	Negative	Negative	Negative	Moderate	Negative	—	No
4	28	M	—	—	1:3200	Moderate	Marked	Moderate	Marked	Negative	Positive	No
5	26	F	—	1:400	1:3200	—	Marked	Moderate	Moderate	Negative	Negative	Yes
6	24	F	Negative	1:200	1:6400	Negative	Marked	Negative	Moderate	Negative	Negative	Yes
7	25	M	Negative	—	1:1600	Negative	Moderate	Moderate	Moderate	Negative	Negative	No
8	28	M	1:25	1:100	1:1600	Negative	Moderate	Moderate	Moderate	Negative	Negative	Yes
9	21	F	—	—	1:1600	Negative	Marked	Moderate	Moderate	Negative	Negative	Yes

Signs

Physical examination in most cases disclosed no abnormalities other than fever and prostration. The temperature charts exhibited by these patients were characterized by great variability. The fevers were usually irregular and intermittent in type, with temperatures highest in the late afternoon, and showing diurnal swings of 1 to 4°. Most patients

TABLE 1 (*Continued*).

Case No.	Chief Symptoms	Dates of Acute Illness	Blood Cultures			Chemotherapy	Blood Levels	Temperature over 99°F.		Present Status of Patient
			Strain	Dates Isolated	Dates Negative			Before Treatment	After Treatment	
							per 100 cc.	*days*	*days*	
1	Moderate fatigue, slight cough, myalgia and moderate headache	Jan. 5–28	*Br. suis*	Jan. 12 Jan. 16 Jan. 24		3,500,000 units of penicillin and 64 gm. of sulfadiazine (Jan. 24–Feb. 5)	7–11 mg.	13	4	Asymptomatic
		Apr. 3–10		Apr. 5 Apr. 6 Apr. 7		None				
2	Moderate fatigue, slight cough, severe headache, generalized arthralgia and myalgia and slight diarrhea	Feb. 3–28	*Br. suis*	Feb. 19	Feb. 17 Feb. 20	2,100,000 units of penicillin and 54 gm. of sulfadiazine (Feb. 24–Mar. 5)	9–10 mg.	7	3	Asymptomatic
3	Marked fatigue, mild photophobia, slight cough, shaking chills, generalized arthralgia and myalgia, moderate nausea and vomiting and severe diarrhea	Mar. 1–Apr. 26	*Br. suis*	Mar. 31 Apr. 3 Apr. 17	Mar. 7 Mar. 13 Apr. 16 Apr. 17 Apr. 18 Apr. 21	810,000 units of streptomycin (Apr. 18–20)	1–3 units	18	9	Persistent fatigue
		May 7–27			May 11 May 15 May 16 May 18 May 19	15,800,000 units of streptomycin (May 19–26)	6–25 units	12	9	
		June 10–Nov. 7			Oct. 19 Oct. 25 Nov. 6	None				
4	Moderate fatigue and generalized myalgia	July 15–28	*Br. suis*	July 16 July 17 July 18	July 19 July 20 July 28	23,000,000 units of streptomycin (July 22–27)	16–47 units	7	6	Unknown
5	Moderate fatigue, slight cough, shaking chills, moderate headache, generalized arthralgia and myalgia and slight nausea	Aug. 6–10			Aug. 7 Aug. 8	None				
		Aug. 17–Sept. 3	*Br. melitensis*	Aug. 18	Aug. 25 Aug. 27 Aug. 28 Aug. 29 Aug. 30	20,500,000 units of streptomycin (Aug. 25–30)	3–28 units	2	9	Asymptomatic
		Sept. 13–27		Sept. 22	Sept. 18 Sept. 19 Sept. 20 Sept. 23 Sept. 24	169 gm. of sulfadiazine (Sept. 24–Oct. 25)	7–15 mg.	10	2	
		Nov. 9–12			Nov. 10 Nov. 14	None				
		Nov. 25–28			Nov. 25 Nov. 26	None				
6	Marked fatigue, slight cough, shaking chills, severe headache, generalized arthralgia and myalgia and moderate nausea and vomiting	Sept. 3–23	*Br. melitensis*	Sept. 8 Sept. 9 Sept. 10 Sept. 12	Sept. 10 Sept. 11 Sept. 12	136 gm. of sulfadiazine (Sept. 10–Oct. 1)	6–14 mg.	7	4	Asymptomatic
		Oct. 7–29		Oct. 12 Oct. 13	Oct. 5 Oct. 8 Oct. 9 Oct. 11 Oct. 12 Oct. 13 Oct. 15 Oct. 23	28 gm. of sulfadiazine (Oct. 13–17)	8–9 mg.	8	17	
7	Marked fatigue, severe headache, generalized arthralgia and myalgia, moderate nausea and vomiting and slight diarrhea	Sept. 29–Oct. 15	*Br. melitensis*	Sept. 22	Sept. 20 Sept. 21 Sept. 23 Sept. 24	177 gm. of sulfadiazine (Sept. 24–Oct. 24)	8–12 mg.	4	3	Persistent fatigue
		Nov. 9–16		Nov. 10	Nov. 12 Nov. 13 Nov. 16	None				
		Nov. 24–Dec. 14		Nov. 30	Nov. 24 Nov. 27 Dec. 1	None				
8	Moderate fatigue, slight headache and generalized myalgia	Sept. 19–Oct. 18	*Br. suis*	Sept. 22 Sept. 24 Sept. 25 Sept. 28	Sept. 29 Oct. 8 Oct. 13 Oct. 24 Oct. 31	180 gm. of sulfadiazine (Sept. 27–Oct. 26)	7–10 mg.	8	5	Asymptomatic
9	Slight fatigue, slight cough and moderate headache	Sept. 10–25			Sept. 11 Sept. 12	164 gm. of sulfadiazine (Sept. 24–Oct. 24)	10–14 mg.	3	1	Asymptomatic
		Oct. 8–29			Oct. 4 Oct. 22	None				

had peak temperatures of 102 to 104°F. during the acute illness. Four patients showed definite periodic undulations of fever, with intervening periods of apyrexia. One patient (Case 11) experienced a four-day episode of sustained high temperature and great prostration, reminiscent of the malignant type of brucellosis. The total number of days of fever — that is, a temperature above 99°F. orally — varied from thirteen to ninety-seven, and averaged thirty-five days. In general, the intensity of symptoms and the degree of prostration were directly proportional to the degree of fever. These descriptions are based on observations made when the patients were not receiving antipyretic drugs.

The spleen could be palpated in only 1 patient (Case 3), and then only after she had suffered pulmonary infarcts. Two patients exhibited moderate generalized abdominal tenderness coincidental with diarrhea. In a few cases, joint pains were accompanied by joint tenderness, but there were no other objective signs of arthritis. Herpes febrilis appeared in 2 cases.

Clinical Course

The course of patients infected with *Brucella suis* was not discernibly different from that of patients infected with *Br. melitensis*. Only one episode of acute illness occurred in 5 patients, two episodes in 9 and three episodes in 2, whereas 1 patient experienced five distinct attacks. In some cases the initial attack was the severest, and in others, subsequent attacks were more prostrating and prolonged. In patients who had an undulating type of fever, the peak of temperature and the intensity of symptoms tended to diminish with succeeding undulations.

TABLE 2. *Summary of Clinical and Laboratory Data in 8 Patients with Acute Brucellosis.*

Case No.	Age	Sex	Agglutinin Titer	Highest Agglutinin Titer		Opsonocytophagic Index				Brucellergen Skin Test		
			Before immunization	After immunization	After infection	Before immunization	Highest reading after immunization	Lowest subsequent reading before onset of illness	Highest reading after infection	Before immunization	After immunization but before illness	Activation after infection
	yr.											
10	26	M	Negative	1:400	1:3200	Negative	Marked	Marked	Moderate	Negative	Negative	Negative
11	27	M	—	1:200	1:3200	—	Marked	Moderate	Moderate	Negative	Negative	No
12	26	M	Negative	1:50	1:3200	Negative	Moderate	Negative	Moderate	Negative	Negative	No
13	26	M	1:25	1:100	1:3200	Slight	Moderate	Moderate	Moderate	Negative	Negative	No
14	21	M	—	—	1:3200	Negative	Negative	Negative	Moderate	Negative	Negative	Yes
15	25	M	Negative	1:25	1:12800	Marked	Moderate	Negative	Marked	Negative	Negative	Yes
16	22	F	—	—	1:1600	Negative	Marked	Marked	Moderate	Negative	Negative	No
17	22	F	—	—	1:2560	Negative	Marked	Moderate	Marked	Negative	Negative	Yes

Increased physical activity was often followed by relapses. Patients were therefore kept in bed during febrile periods and were permitted only gradual increases in activity during convalescence. The convalescent period was long because of a persistent state of lassitude and easy fatigability that lasted for months after all other evidence of illness had disappeared. The shortest illness was observed in Case 2, in which the patient had recovered, apparently completely, four months after the onset. The longest illness was observed in Case 3, and after twelve months the patient continues to have occasional symptoms. Five of the other patients still complain of easy fatigability five to twelve months after the onset of disease. None of the patients exhibited signs of localized Brucella infection in any particular organ or system.

Laboratory Data

Blood Cultures

In taking blood cultures, two types of medium were used routinely. On each occasion, 15 cc. of blood was withdrawn, of which half was added to 100 cc. of nutrient broth and half to 100 cc. of Bacto-Tryptose broth. All blood cultures were incubated under aerobic conditions at 37°C., and were subcultured repeatedly on tryptose-agar plates. All cultures were held for fourteen days before being discarded. In the majority of cases the organisms grew equally well in both mediums. When specimens were taken during sulfadiazine therapy, 5 mg. of para-aminobenzoic acid was added to each 100 cc. of medium. When cultures were taken during streptomycin therapy, 25 mg. of cysteine hydro-

TABLE 2 (*Continued*).

Case No.	Chief Symptoms	Dates of Acute Illness	Blood Cultures			Chemotherapy	Blood Levels	Temperature over 99°F.		Present Status of Patient
			Strain	Dates Isolated	Dates Negative			Before Treatment	After Treatment	
10	Moderate fatigue, generalized arthralgia and myalgia	Sept. 5–13 Oct. 28–Nov. 3	*Br. melitensis*	Sept. 11	Sept. 11 Oct. 19	139 gm. of sulfadiazine (Sept. 18–Oct. 11) None	5–12 mg.	0	0	Asymptomatic
11	Marked fatigue, moderate cough, shaking chills, severe headache, generalized arthralgia and myalgia, moderate nausea and vomiting and severe diarrhea	Aug. 13–Sept. 15 Sept. 28–Oct. 18	*Br. melitensis*	Aug. 26 Aug. 27 Aug. 30 Aug. 31 Oct. 12 Oct. 13 Oct. 15 Nov. 8	Oct. 5 Oct. 25 Nov. 5 Nov. 15	151 gm. of sulfadiazine (Aug. 30–Sept. 24) 50 gm. of sulfadiazine (Oct. 13–20)	9–15 mg. 9–15 mg.	10 1	9 4	Persistent fatigue
12	Moderate fatigue, shaking chills, slight headache and generalized arthralgia and myalgia	Sept. 9–26 Nov. 5–Dec. 5	*Br. suis*	Sept. 14 Sept. 16 Nov. 6 Nov. 8 Nov. 16 Nov. 21 Nov. 26 Dec. 8	Sept. 12 Sept. 15 Nov. 9 Nov. 12 Nov. 23 Nov. 25 Dec. 8	137 gm. of sulfadiazine (Sept. 19–Oct. 11) None	5–10 mg.	7	4	Asymptomatic
13	Marked fatigue, shaking chills, moderate headache, generalized arthralgia and myalgia and moderate nausea	Aug. 27–Sept. 3 Sept. 28–Dec. 12	*Br. suis*	Aug. 31 Sept. 1 Oct. 4 Oct. 5 Oct. 21 Oct. 22 Oct. 23 Oct. 29 Nov. 4 Nov. 7 Nov. 21 Dec. 3	Nov. 26 Dec. 6	132 gm. of sulfadiazine (Sept. 1–21) None	9–14 mg.	1	3	Asymptomatic
14	Marked fatigue, shaking chills, moderate headache and generalized arthralgia and myalgia	Sept. 22–Oct. 2 Nov. 20–Dec. 7	*Br. suis*	Sept. 28 Sept. 29 Oct. 4 Dec. 1	Sept. 30 Oct. 9 Dec. 2 Dec. 8 Dec. 20	173 gm. of sulfadiazine (Sept. 29–Oct. 28) None	6–14 mg.	2	3	Asymptomatic
15	Marked fatigue, severe headache, generalized arthralgia and myalgia and moderate nausea and vomiting	Oct. 10–29 Nov. 28–Jan. 3	*Br. melitensis*	Oct. 17 Oct. 18 Oct. 20 Oct. 21 Dec. 1 Dec. 7	Oct. 30 Nov. 30 Dec. 2 Dec. 16 Dec. 18 Dec. 31	172 gm. of sulfadiazine (Oct. 18–Nov. 16) None	7–13 mg.	7	11	Persistent fatigue
16	Moderate fatigue, shaking chills and moderate headache	July 22–Aug. 17	*Br. melitensis*	July 27 July 28 July 29 July 30	July 24 July 31 Aug. 10	None				Persistent fatigue
17	Moderate fatigue and generalized arthralgia and myalgia	Oct. 20–Nov. 26			Oct. 25 Nov. 2	None				Asymptomatic

chloride was added to each 100 cc. of medium to inhibit the action of this antibiotic.

Br. suis was isolated from the blood in 8 cases, and *Br. melitensis* in 7. One or more positive blood cultures were obtained in most patients during the initial acute phase of illness, and usually again during subsequent febrile relapses. It is worth emphasizing the fact that blood cultures were occasionally positive during periods when symptoms were minimal and when temperatures were normal throughout the day.

Agglutination Tests

The macroscopic tube-agglutination technic used in the United States Army[2] was employed. The antigen was a standardized suspension of *Br. abortus* prepared at the Army Veterinary School. Titers were expressed in terms of the highest final dilution of serum at which agglutination was visible with the aid of a concave magnifying mirror (Table 1). Prior to immunization no titer exceeded 1:25, and after immunization none exceeded 1:400. This serologic response to immunization usually fell after one or two months.

In all patients there was a sharp rise in agglutinins within three or four weeks of the onset of illness. Maximum titers of 1:1600 to 1:12,800 were reached in one or two months, after which the titers usually dropped slowly. After six months the agglutinin titers varied from 1:400 to 1:1600.

The height of the agglutinin titer was not proportional to the severity of illness, nor did it show consistent variations with remissions or exacerbations. It can be said that agglutinin determinations were useful for diagnosis but not for prognosis.

Opsonocytophagic Index

This test* was performed essentially as outlined by Huddleson.[3] The opsonocytophagic index was usually altered by immunization so that the interpretation of subsequent determinations was difficult. Table 1 shows that the indexes increased in 9 patients after infection as compared with preinfection determinations, whereas in 8 patients they remained at the same level or actually fell. In this series the opsonocytophagic index was therefore of questionable diagnostic value. As with the agglutination test, the index showed no predictable variation with alterations in clinical course and thus did not aid in prognosis.

Skin Tests

None of the 17 patients showed skin sensitivity to 0.1 cc. of undiluted brucellergen administered intradermally prior to immunization. The test was repeated after immunization and in one patient was positive. Skin tests were not performed after the onset of illness because of the danger of precipitating systemic reactions during the course of active infection. A phenomenon of great interest was observed in 8 patients: after the onset of clinical illness erythema and edema appeared spontaneously at the sites of the previous skin tests and vaccine injections, and in 1 case the inflammatory lesion progressed to actual necrosis. It must be emphasized that these delayed inflammatory phenomena developed in 6 patients from four to six months, and in 2 patients one and sixteen months, respectively, after the administration of the brucellergen or vaccine. The lesions appeared during the acute illness, faded during remissions, and reappeared with subsequent exacerbations.

Chest X-Ray Examination

Roentgenograms were taken routinely on admission and at intervals thereafter. They were consistently normal, except in Case 3, in which the patient, while receiving continuous intravenous streptomycin therapy, developed thrombophlebitis followed by bilateral pulmonary infarcts.

White-Cell Counts

The blood in all cases showed a leukopenia with a relative lymphocytosis. This finding frequently persisted beyond the stage of acute illness. There were no abnormal cell forms.

Treatment

A summary of the treatment in these cases is presented in Table 1. Eleven patients received sulfadiazine, 2 were given penicillin and sulfadiazine simultaneously, 3 received streptomycin, and 2 were given only symptomatic therapy. One patient (Case 5), who was given a course of sulfadiazine during a relapse following streptomycin therapy, is included in both groups. The table shows the duration of fever before and after initiation of chemotherapy for each patient. These figures cover the span of a single acute episode and afford a rough index of the clinical response to the given chemotherapeutic agent.

Sulfadiazine Therapy

Unpublished experimental data from the technical laboratory at this station indicated that thirty days of sulfadiazine therapy in guinea pigs infected with *Br. suis* resulted in a definite modification of the disease. Because of these encouraging results, 11 patients were treated with sulfadiazine for periods of twenty to thirty days. Blood levels of free sulfadiazine were maintained well in excess of concentrations required to inhibit the growth of *Br. suis* in vitro. There was no clear-cut, abrupt amelioration of symptoms; the temperatures dropped to normal in one to eleven days after the beginning of treatment. In all but 1 of these 11 patients, after the

*The cells were categorized according to the degree of phagocytosis, as "negative," "slight," "moderate" or "marked," according to Huddleson's criteria. The category containing the greatest number of cells was then taken as the final reading for the slide. When two categories contained an equal number of cells, the two remaining categories were considered in determining the final reading.

temperature had returned to normal, there were no marked elevations during the remainder of the therapeutic period. Ten patients had positive blood cultures prior to treatment. Blood cultures were taken during treatment in 6 cases and were positive in 4, on the second to sixth days of treatment. The evaluation of therapeutic efficacy of a drug is admittedly difficult in a disease whose course is as variable as that of brucellosis. Nevertheless, there seemed little clinical evidence that sulfadiazine therapy had benefited these patients. There was in fact ample evidence that none of them had been cured, for all 11 patients in this group suffered one or more relapses after cessation of therapy. During these relapses, blood cultures were positive in 7 cases, negative in 3 and were not taken in one.

Strains of Brucella isolated before, during and after therapy were tested in vitro for sensitivity to sulfadiazine. There was no demonstrable decrease in sensitivity as a result of therapy.

Simultaneous Administration of Sulfadiazine and Penicillin

The 2 patients in this group received treatment for twelve and nine days respectively. Penicillin was given intramuscularly, and sulfadiazine by mouth. In neither case was there a definite clinical response to therapy. One patient (Case 1) had a short relapse with positive blood cultures subsequent to treatment; since that time she has been well. The other (Case 2) has apparently recovered completely.

Streptomycin Therapy

Streptomycin hydrochloride* was submitted to clinical trial in 3 cases. Studies of absorption and excretion of streptomycin in these patients are reported elsewhere.[4] The drug was administered intramuscularly or intravenously. There was no apparent clinical response in these patients. All 3 had positive blood cultures prior to treatment, and 2 (Cases 3 and 5) had negative cultures during treatment. No blood cultures were taken during treatment in the third case. In Cases 3 and 5 the patients had one or more relapses, one with positive blood cultures and the other without. The subsequent course in Case 4 has not been ascertained, since we were unable to observe the patient following recovery from the initial episode.

*Kindly supplied by Merck and Company, Rahway, New Jersey.

Symptomatic Therapy

As stated above, the symptoms in most patients were directly proportional to the degree of fever. It was found that acetylsalicylic acid in doses of 0.3 to 0.6 gm. administered regularly every four hours resulted in a sharp drop in fever and a coincidental decrease in malaise, muscular aching and headache.

Summary and Conclusions

Clinical and laboratory data from 17 cases of brucellosis are presented. The patients were laboratory workers engaged in investigative work with strains of *Brucella suis* and *Br. melitensis*.

Eleven patients were treated with sulfadiazine for periods of twenty to thirty days. There was no evidence that this therapy altered the natural course of the disease. Of the remaining patients, 3 were treated with streptomycin, and 2 with penicillin and sulfadiazine simultaneously. From this limited clinical experience there was no indication that these drugs were of therapeutic benefit.

Addendum. The status of 14 out of these 17 patients was ascertained as of January 1, 1947, approximately two years after the occurrence of the first case. The status of 3 patients (Cases 2, 10 and 17) is unknown. One patient (Case 3) has had more than ten febrile episodes since the onset of her illness, and continues to experience severe symptoms. Three patients (Cases 4, 13 and 16), who are back at normal activity and no longer exhibit fever, report mild occasional symptoms. The remaining 10 patients are well, following illnesses lasting from one to twelve months (average, slightly less than six months).

References

1. Meyer, K. F., and Eddie, B. Laboratory infections due to Brucella. *J. Infect. Dis.* 68:24-32, 1941.
2. *Laboratory Methods of the United States Army.* Edited by J. S. Simmons and C. J. Gentzkow. Fifth edition. 823 pp. Philadelphia: Lea & Febiger, 1944.
3. Huddleson, I. F., Hardy, A. V., Debono, J. E., and Giltner, W. *Brucellosis in Man and Animals.* Second edition. 379 pp. New York: Commonwealth Fund, 1943.
4. Kornegay, G. B., Forgacs, J., and Henley, T. F. Studies on streptomycin. II: Blood levels and urinary excretion in man and animals. *J. Lab. & Clin. Med.* 31:523-534, 1946.

MEDICAL PROGRESS

STREPTOMYCIN (Concluded)*

II. Clinical Uses

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BOSTON

THE present knowledge of the clinical usefulness of streptomycin is largely the result of a coordinated effort by the streptomycin producers with the medical departments of several governmental agencies, including the Army, Navy, Public Health Service and Veterans Administration, as well as many physicians throughout the country. Under the guidance of the Committee on Chemotherapeutics and Other Agents of the National Research Council and with funds contributed by several pharmaceutical and chemical companies, limited amounts of streptomycin were apportioned to civilian physicians for the purpose of investigating its effectiveness in a wide variety of conditions. Much valuable information was thus accumulated in a short time, although there is still need for further investigation.[202] The practical aspects of streptomycin administration, the results of treatment of various infections and the toxic effects observed are considered below.

ADMINISTRATION AND DOSAGE

Streptomycin, as either the hydrochloride or the sulfate, is usually supplied as a dry, sterile powder in airtight rubber-capped vials each containing the equivalent of 1.0 gm. (1,000,000 units) of the streptomycin base. Streptomycin and its salts are reasonably stable, but storage at a temperature not above 15°C. is recommended. Solutions are less stable than the dry powder and should be kept in a refrigerator.[40]

Streptomycin may be administered parenterally, orally or locally. The intramuscular route is the one generally used for parenteral administration. The subcutaneous route may be used, but it is likelier to cause pain and local irritation. Intravenous injections are used chiefly to attain high concentrations rapidly or to avoid local irritation; immediate systemic reactions, however, are more frequent with this route.[202] Various investigators have given the drug orally.[45, 183, 202, 203] Topically, streptomycin has been applied intrathecally,[72, 80, 81, 119, 202, 204, 205] intracisternally,[206] into the lateral cerebral ventricles, through the anterior fontanelle, in infants,[81] intrapleurally,[205, 207] intraperitoneally,[202] cystoscopically into the urinary bladder and kidney pelves,[81] by inhalation,[82, 202, 208] intratracheally,[209] by gauze soaks to cutaneous areas[74] and by drops on the conjunctiva,[210, 211] into the nose [212] and into the external auditory canal.[82]

Parenteral Administration

The object of parenteral streptomycin is to maintain an inhibitory concentration in the blood stream and at the sites of infection. The concentration of streptomycin required to inhibit different bacteria varies considerably, and clinical results do not always correspond to the in vitro sensitivity of the bacteria.[57, 62, 84, 145, 203] On general principles, it seems wise to administer large doses of streptomycin and thus to maintain high blood and local concentrations.[202, 213–216] In adults the intramuscular administration of 1.0 gm. of streptomycin at six-hour intervals is ordinarily adequate for most infections. This dose is usually well tolerated and provides a good margin of therapeutic safety, but smaller doses have generally been used.[202] Somewhat larger doses — up to 8 gm. a day — may be given to adults if indicated.¶ Infants and children require smaller doses; 30 to 75 mg. per pound of body weight, or a total of 0.25 to 2.0 gm. daily should be adequate.[80, 81, 204]

Intermittent intramuscular injection is the parenteral method of choice. The gluteal regions, the lateral aspects of the thighs and sometimes the triceps muscle may be used in rotation. Each gram of streptomycin is dissolved in 4 or 5 cc. of sterile, pyrogen-free distilled water or physiologic saline solution. This volume can be administered with only slight discomfort to the patient, but, if desired, 1 cc. of 1 per cent procaine hydrochloride may be added to each 4 cc. of streptomycin solution. A more dilute solution — 0.1 gm. per cubic centimeter — may be used for intramuscular injections of 0.5 gm. or less. The solution should be clear and free of undissolved particles.[202] For continuous intra-

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¶It has been stated that infections will not be influenced, regardless of the amount of streptomycin given, if the infecting organism grows in 16 microgm. per cubic centimeter, and, furthermore, that no additional benefit may be expected, regardless of the type or severity of the infection, from doses greater than 3.0 gm. a day.[48] This is at variance with our experience.

venous administration 1 or 2 gm. may be dissolved in a liter of physiologic saline solution and given at the rate of about twenty-five drops a minute. For single or intermittent intravenous injections, 1.0 gm. of streptomycin is dissolved in 20 cc. or more of physiologic saline solution and injected slowly.[85]

Oral Administration

Streptomycin is absorbed only to a slight extent after its ingestion, and little appears in the bowel contents during parenteral administration. The ingestion of 2 to 5 gm. daily in orange juice or other liquids is well tolerated and produces a marked reduction in the number of most of the susceptible organisms in the feces.[84, 202] The method has been used in preparing patients for operations on the bowel.[86, 217]

Local Administration

Intrathecal injection. Since adequate diffusion of streptomycin from the blood into the cerebrospinal fluid cannot be relied on,[69–73, 218, 219] systemic therapy should be supplemented by local administration in the treatment of meningitis. Doses of 50 to 200 mg. dissolved in 5 to 10 cc. of physiologic saline solution may be given intrathecally every twelve to forty-eight hours.[202, 204, 205] Injections of more than 50 mg., however, may produce signs of meningeal irritation.[72, 81, 119, 206] As much as 25 mg. a day has been given intraspinally, intraventricularly or directly into a meningocele sac in infants who were about two weeks old.[81] Streptomycin has been injected safely into infected lateral cerebral ventricles[81] and into the basal cistern.[220]

Inhalation. Streptomycin may be administered for bronchopulmonary disease either as an aerosol[82, 208] or by intratracheal instillation.[209] Doses of 50 to 100 mg. in 1 cc. of physiologic saline solution may be nebulized at intervals of two to six hours.[82, 202] More concentrated solutions are unsatisfactory for aerosols and are wasteful because their viscosity causes frothing and because the nebulizer tends to clog.

Other routes. Streptomycin has been applied directly to the urinary bladder and kidney pelves through a cystoscope or an indwelling catheter,[31] but such an approach offers no advantage over parenteral therapy since the drug is usually excreted in a high concentration in the urine. The antibiotic has been injected intrapleurally in the treatment of empyema.[202, 205] The optimum dosage by this route is not known, but 50 to 500 mg. in 25 to 100 cc. of physiologic saline solution can probably be introduced safely into the infected pleural cavity. As much as 1 gm. has been put into the peritoneal cavity at the time of operation.[74] Solutions containing 10 mg. per cubic centimeter have been applied to the conjunctiva (two drops every four hours) without harmful effects.[210, 211] Streptomycin in concentrations up to 25 mg per cubic centimeter has been instilled into the auditory canals of patients with suppurative otitis without ill effects.[221] It has been used as nose drops in a concentration of 10 mg. per cubic centimeter, five drops being administered into each nostril every three hours.[212] It has been applied locally to wounds in concentrations of 0.2 to 0.5 mg. (200–500 units) per cubic centimeter.[74]

URINARY-TRACT INFECTIONS

Streptomycin has been used extensively in the treatment of urinary-tract infections.[31, 80, 74, 84–86, 194, 202, 203, 212–214, 222–228] The report of the National Research Council[202] includes 409 cases with an overall recovery rate of 42 per cent based mostly on short periods of observation. Similar results were obtained in 264 cases treated in Army hospitals.[225] Almost all civilian patients had previously been treated ineffectively with sulfonamides and penicillin. A considerable number improved during streptomycin treatment but then relapsed, generally during the first week after cessation of therapy.

Several points have been emphasized. Many patients show definite clinical improvement without bacteriologic remission. Many who improve are cured bacteriologically but do not recover clinically because the underlying anatomic irregularities are not corrected. Infections due to a single organism respond oftener than mixed infections do. Rapid development of resistance during treatment is frequent and accounts for many of the failures. A minimal follow-up period of a week is essential before any patient with a urinary-tract infection can be considered recovered. All cases should be carefully studied to determine the nature of the infection, the sensitivity of the organisms, the reaction of the urine and the presence of underlying anatomic lesions.[202, 213]

In the treatment of urinary-tract infections in patients with neurogenic bladders following spinal injuries streptomycin has proved useful only for controlling the severe infections and associated septicemias.[31, 194, 225] In such cases only 28 per cent of patients improved, as compared with 54 per cent among those without spinal-cord injuries.[225] Streptomycin-resistant strains often developed in these cases, and even when this did not happen, cessation of therapy was promptly followed by the appearance of new infections. There was no advantage in the use of streptomycin locally.[31]

Alkalinization of the urine may be an important adjunct to streptomycin therapy of urinary-tract infections because of the increased activity of streptomycin in an alkaline medium.[60] In 21 cases studied at the Boston City Hospital the first 7 patients were treated without alkalies, and failures in 6 cases were associated with the development of highly resistant strains of bacteria during treatment.[85] On similar doses of streptomycin, usually 4 to 6 gm. daily, but with alkalinization of the urine

during the streptomycin treatment in the remaining 14 cases, 8 patients were cured and 6 were temporarily improved. Only 1 of the latter developed a resistant organism during treatment, and the other 5 had recurrences of infection following the cessation of streptomycin, possibly because of uncorrected anatomic defects in the urinary tract. These patients were followed for two to four months. Alkalinization of the urine was usually accomplished by the oral administration of 1 gm. each of sodium bicarbonate and potassium citrate every four hours, but larger doses were sometimes required. The urine was checked frequently during therapy to ensure that an alkalinity actually existed.

Albright[229] has had good results with streptomycin in cases of urinary infections associated with renal stones. Alkalinization with sodium citrate was used routinely in his cases. Kane and Foley[230] treated 40 cases due to gram-negative bacilli at the Massachusetts General Hospital and followed them for four to eight months. Cures were obtained in 30 cases; 4 patients were improved, and 6 cases were failures. Alkalies were given to all, and a resistant strain developed in only 1 case.

Infections of the Central Nervous System

Streptomycin has proved of great value in the treatment of infections of the central nervous system due to gram-negative bacilli. It has been used most extensively in meningitis caused by *Haemophilus influenzae*.

Meningitis due to H. Influenzae

The report of the National Research Council[202] includes 100 cases: 66 of the patients were cured clinically and bacteriologically while under treatment; 13 improved under treatment and finally recovered; 1 improved but relapsed; 3 showed no effect; and 17 died. Eighteen of the 66 patients who recovered received streptomycin alone; the others received, in addition, various combinations of sulfonamides, penicillin and antiserum. The average daily dose of streptomycin was 0.5 gm. intramuscularly and 60 mg. intrathecally.

Several authors[57, 70, 75, 80, 81, 119, 203, 204, 206, 218, 219, 225, 227, 231, 232] have reported cases of *H. influenzae* meningitis that were treated with streptomycin, and many of these cases were probably included among the 100 mentioned above. Analysis of the individual reports, however, yields valuable information. When streptomycin therapy alone was instituted early in the course of the disease and in adequate amounts, the results were almost uniformly favorable.[80, 203] When the treatment was begun late in the disease, the results were quite irregular. The findings indicate that streptomycin alone, in adequate doses intramuscularly and intrathecally, is effective if the treatment is begun early in the course of the disease; sulfadiazine and antiserum should also be used when treatment is started late. The streptomycin should be given for at least seven days.[218]

The development of streptomycin-resistant strains of *H. influenzae* has been noted in 4 cases during the course of treatment.[80, 119, 203] This untoward phenomenon should be looked for at the first sign of a recrudescence of clinical symptoms and signs or when *H. influenzae* reappears in the cerebrospinal fluid. Sulfadiazine and specific rabbit antiserum should then be added to the therapeutic regime. The occurrence of secondary infections during streptomycin treatment must be watched for constantly and treated vigorously as soon as recognized. Complicating staphylococcal infections were reported in 3 children under streptomycin treatment for *H. influenzae* meningitis.[204] One of them died of staphylococcal pneumonia, despite added penicillin therapy; the second had an acute otitis media, and the third had a meningitis due to a staphylococcus, and both responded favorably to penicillin.

Meningitis Due to Miscellaneous Gram-Negative Bacilli

There are reports of streptomycin treatment in cases of meningitis due to the following gram-negative bacilli: *Aerobacter aerogenes*,[225] *Alcaligenes faecalis*,[202] *Escherichia coli*,[202, 218, 220, 225, 233] *Proteus morganii*,[81, 202] *Pr. vulgaris*,[225] *Klebsiella pneumoniae*,[202, 234] *Salmonella choleraesuis*,[202, 235] *Pseudomonas aeruginosa*[81, 206, 225] and an achromobacterium.[206] The over-all mortality rate in these cases was high, but inspection of the data shows that when streptomycin therapy was instituted early in the course of the disease and given intrathecally as well as parenterally in adequate doses, the results were favorable. Infections of the central nervous system by gram-negative bacilli respond poorly to sulfonamides and little if at all to penicillin. The early and proper use of streptomycin in such cases may therefore be life saving.

Brain Abscess

Of 4 cases treated in Army hospitals, 3 patients improved, but only when parenteral streptomycin therapy was supplemented by drainage of the abscess and local instillation of streptomycin. Both gram-negative bacilli and gram-positive cocci were cultured in these cases.[225] Improvement was noted in an additional case.[202]

Infections of the Respiratory Tract

Acute Infections

H. influenzae and *K. pneumoniae* are the only gram-negative bacilli—except in cases of tularemia, plague and glanders — that are important causes of primary acute pulmonary infections. Such infections are infrequent in adults, are usually superimposed on a chronic bronchiectasis or chronic bronchitis and generally respond poorly to sulfon-

amide or penicillin treatment. Infections due to *H. influenzae* may be frequent and serious in infants and children. Several streptomycin-treated cases due to these organisms have been reported.[74, 82, 202, 203, 209, 218, 236–238] A few cases of acute pneumonitis, apparently due to *H. influenzae*, responded favorably to streptomycin after failing to improve on sulfonamides and penicillin.[82, 209, 218] The institution of streptomycin therapy in these patients was followed by prompt clinical improvement and disappearance of *H. influenzae* from the sputum.

Pneumonia due to Friedländer bacillus has a high mortality rate[239] that has not been strikingly influenced by sulfonamides or penicillin. The response to streptomycin in such cases has not been uniformly favorable,[74, 82, 202, 225, 240] in spite of the fact that the causative organism, *K. pneumoniae*, is usually quite sensitive to the drug. The results are readily understandable when one considers the pathology of this disease, which is marked by the early development of multiple pulmonary cavities filled with viscid exudate. Four cases of pneumonia due to Friedländer bacillus have been reported in which streptomycin therapy begun after several days of ineffective sulfonamide or penicillin therapy, or both, resulted in prompt improvement.[203, 218, 226, 237] One case is reported in which a resistant strain of *K. pneumoniae* developed in the sputum after two days of streptomycin therapy; the patient nevertheless improved promptly and eventually recovered.[82] In view of the high mortality in pneumonia due to Friedländer bacillus, the prompt institution of large doses of streptomycin — preferably 1.0 gm. every four hours in adults — seems indicated.

In a case of severe pharyngitis apparently due to *Ps. aeruginosa* in a child with leukemia, the organisms quickly disappeared from the throat following institution of streptomycin therapy.[203]

Chronic Infections

Chronic bronchiectasis is a distressing and debilitating disease. Treatment of such cases with penicillin aerosol in conjunction with postural drainage has proved to be of much help in reducing the amount of sputum, decreasing the incidence and severity of the episodes of superimposed pneumonitis and in preparing the patients for operations.[241] Penicillin, however, eliminates only the penicillin-sensitive organisms, and in some patients the infection persists, owing to the presence of the penicillin-insensitive organisms, mostly gram-negative bacilli. The response of such cases to streptomycin has been encouraging.[82, 208, 209, 218] The volume of sputum diminishes, and gram-negative bacilli disappear promptly following inhalations of streptomycin aerosol.[208] The total daily dose of nebulized streptomycin used in some of these cases was 0.5 gm. in 20 cc. of saline solution daily.[208] Similar cases have been treated by daily intratracheal instillations of 5 cc. of streptomycin solution containing 10 mg. per cubic centimeter, with similar favorable results.[209]

The ease of administration of antibiotics by aerosol offers a simple but often effective means of treating patients with chronic bronchiectasis and chronic bronchitis. Whether or not concomitant parenteral therapy in these patients is advantageous has not been determined, and the problem of development of resistance by the organisms under aerosol treatment must be investigated further.[82] The rational aerosol treatment of chronic bronchiectasis may well involve the combined use of penicillin and streptomycin.[208] Such treatment is probably only palliative but may offer considerable relief from the distressing symptoms, lessen the frequency of complications and possibly arrest the progress of the disease.

Empyema

Several cases of empyema thoracis have been treated with variable results. Details in these cases are lacking.[202, 225]

Nasal and Sinus Infections

A case of chronic sinusitis due to *K. pneumoniae*[117] was treated with 100 mg. of streptomycin aerosol five times daily given by the method of Barach and his associates.[242] The patient had undergone two episodes of pneumonia due to Friedländer bacillus during the previous two years. The Friedländer bacilli were promptly eliminated from the nose and sputum. Four patients with ozena possibly due to *K. pneumoniae* were treated by parenteral streptomycin, with symptomatic improvement.[243]

Bacterial Endocarditis

There are few reports on the use of streptomycin in bacterial endocarditis. Although endocarditis due to gram-negative bacilli is infrequent, the early use of streptomycin in such cases seems indicated. The only reported recovery occurred in a case of subacute bacterial endocarditis due to an unidentified gram-negative bacillus.[244] Streptomycin therapy was started in that case after several days of treatment with penicillin and sulfadiazine. Although cultures had already become negative, it was thought that the streptomycin helped effect the cure.

The usefulness of streptomycin in endocarditis, however, may not be limited to infections with gram-negative bacilli. Indeed, the drug may be superior to penicillin in certain infections, such as those due to enterococci and nonhemolytic or alpha-hemolytic streptococci, that are resistant to the concentrations of penicillin maintained in the blood but sensitive to those attainable with streptomycin. Three cases of subacute bacterial endocarditis caused by such organisms were reported.[122] Two of them were due to nonhemolytic streptococci that were inhibited by 1 unit of streptomycin but required 6 units of penicillin in one case and 4 units in the other. Treatment with streptomycin was

successful in the first case after five weeks of penicillin had proved ineffective. The second case was also treated with streptomycin after an unsuccessful course of penicillin. Blood cultures in this case were negative during streptomycin therapy, and the patient eventually recovered despite two positive blood cultures obtained after the streptomycin had been stopped. In the third case the organism was a strain of *Streptococcus viridans* that was inhibited by 0.8 units of penicillin and 0.1 units of streptomycin per cubic centimeter. Penicillin had produced no effect in this case. The patient died after five days of streptomycin treatment, but at autopsy no bacteria were found in the vegetations on the heart valves. In these 3 patients the dosage of streptomycin was small — only 0.5 gm. a day. A fourth case, due to *Str. faecalis*, was treated unsuccessfully.[245, 246]

In cases of subacute bacterial endocarditis due to gram-positive cocci that do not seem to respond to penicillin, the sensitivity of the organism to both penicillin and streptomycin should be determined if possible, and streptomycin treatment instituted if the organism is found to be insensitive to penicillin but sensitive to streptomycin. The dose in such cases should be large, preferably about 1.0 gm. intramuscularly every four hours for adults.

Enteric Infections

Typhoid Fever

Streptomycin has not been particularly effective in the treatment of typhoid fever or of typhoid carriers. Fifty-one cases of typhoid fever were included in the report of the Committee on Chemotherapeutics and Other Agents.[202] The majority of these patients received 4.0 gm. of streptomycin daily for seven or eight days without a favorable effect on the course of the disease. Combined oral and intramuscular therapy was used in 15 cases, with results that were no better than those in the cases treated by intramuscular injections alone. Others[70, 84, 203, 213, 218, 225, 240, 247, 248] have reported similar results. Oral and intramuscular streptomycin was ineffective in clearing up typhoid carriers.[183, 248]

A case in an eighteen-year-old girl[249] is worth citing. Treatment was begun on the twenty-seventh day of illness with 1.0 gm. intramuscularly every four hours. This was increased to 1.5 gm. every four hours after six days and then to 2.0 gm. every four hours after another five days, and the latter dosage was continued until the patient died on the fortieth day. During the last five days of life, 3.0 gm. of streptomycin was also given orally each day. Blood cultures eventually became negative, but stool cultures remained positive for *Eberthella typhosa* during this treatment. *Esch. coli*, however, disappeared from the stool cultures during this period. Strains of *E. typhosa* obtained from the stool and blood after eight days of therapy were sensitive to 16 units. At autopsy, typhoid bacilli were grown from the blood, intestinal ulcers, urine and bile. The patient died despite intensive therapy, although the infection was due to an organism that was moderately sensitive in vitro.

Salmonella Infections

Streptomycin therapy of Salmonella infections has also been generally unsuccessful,[70, 145, 202, 203, 213] although some cases may have been favorably influenced.[202, 250] In 26 collected cases 10 patients recovered during treatment, 2 improved during treatment and later recovered, 6 showed no improvement and 8 died.[202] The treatment of enteritis due to *S. typhimurium* in 5 newborn infants has been reported.[145] Streptomycin was given orally to 4 and both orally and intramuscularly to 1 patient. There was little noticeable effect on the clinical course. The normal fecal flora and the pathogens were suppressed by oral doses of 25 to 100 mg. every three hours for four days. The organisms reappeared promptly after the end of treatment. No increase occurred in the resistance of the organisms. Further trials of streptomycin with early and prolonged use of large parenteral and oral doses may be indicated in these infections.

Shigella Infections

In a case of bacillary dysentery due to *Shigella sonnei* streptomycin was given by mouth in doses of 1.0 gm. five times daily for four days. The diarrhea and fever subsided in twelve hours, and the causative organisms disappeared promptly from the stools.[203] This seemed to be a dramatic response to oral streptomycin alone. Two additional patients with bacillary dysentery due to Shigella responded promptly to streptomycin treatment, and stool cultures became negative.[202] Prolonged sulfonamide therapy had previously been ineffective in these cases. A prompt response was reported in 5 other cases.[225]

Cholera

In 8 Chinese patients suffering from cholera who were treated with streptomycin in doses of 4 gm. daily by mouth supplemented by an occasional intravenous dose, there was little indication that the streptomycin offered any clinical advantages over the use of hydration or sulfonamides, or both.[134] The number of cholera organisms in the stools was apparently reduced promptly and markedly following oral streptomycin, although some were still present by culture and their resistance to streptomycin had increased from 5 to 500 units.

Biliary-Tract Disease

There are reports of 5 cases of cholangitis, with or without cholecystitis, and 2 cases of liver abscess treated with streptomycin, in all of which the patients improved.[202] A patient with cholecystitis

improved with streptomycin, but only after cholecystectomy.[225] In a case of liver abscess due to an anaerobic hemolytic streptococcus the patient improved, also after surgical drainage.[225] Observations on the excretion of streptomycin in such cases indicate that, for the drug to be effective in cholecystitis or cholangitis, it is necessary that liver function be unimpaired and biliary drainage be free.[89, 90]

Peritonitis

The reported results of streptomycin therapy in peritonitis are quite variable, as might be expected. Controlled observations in animals and some highly favorable clinical results suggest that it may be of value in cases of peritonitis due to susceptible organisms. In dogs, the mortality from experimental peritonitis was reduced from 70 per cent in controls to 40 per cent in subjects treated with streptomycin.[88] In another study, however, better results were obtained in dogs with the use of penicillin and sulfonamides than with streptomycin.[86] In a collected series of 53 human cases of peritonitis of varied etiology, there were 39 recoveries, 12 deaths and 2 cases in which there was no effect. Most of these patients received 1 or 2 gm. daily for eight days, and more than half of those who recovered also received other forms of chemotherapy. In this series there were only 3 deaths in 21 cases complicating appendicitis.[202]

No spectacular effects were reported from streptomycin on the course of peritonitis in 12 patients, most of whom also received penicillin in what may now be considered small doses. There was only 1 death among 7 cases in which the peritonitis was secondary to appendicitis, and 1 death in 5 cases that were secondary to perforated peptic ulcers. Coliform organisms were most frequent in cultures of the former, and alpha-hemolytic streptococci predominated in the latter.[74] In Army hospitals, about 80 per cent of the streptomycin-treated cases of peritonitis recovered, but the infection had already been localized in half the cases when the streptomycin therapy was started.[225]

A prompt response to streptomycin was noted in 2 isolated cases, one due to a colon bacillus[281] and the other to *Ps. aeruginosa*.[203] A third case of peritonitis associated with a ruptured appendix was treated successfully with streptomycin in conjunction with appendectomy and surgical drainage.[243] Good results were also noted from streptomycin given prophylactically to 2 patients in whom the peritoneum was accidentally contaminated during an operation.[74]

Streptomycin may be useful as a prophylactic agent in the preparation of patients for large-bowel surgery because of the marked reduction in the intestinal flora that follows its oral administration. This reduction is usually greater than that following succinylsulfathiazole,[86] but occasionally it may not occur.[217]

The optimum treatment of peritonitis may involve the simultaneous use of large doses of both penicillin[262] and streptomycin, with the realization that in the presence of pocketed collections of pus the response to therapy may be slow but that complications may be avoided and the eventual duration of the disease shortened.

Infections of the Eye

Good results were reported in 9 patients with corneal ulcers treated by streptomycin solutions placed on the conjunctiva.[211] There were no bacteriologic reports in these cases, but gram-negative bacilli may cause such infections.[288] One patient[210] with a severe corneal ulcer due to *Esch. coli* responded quickly to streptomycin after treatment with penicillin intramuscularly and locally and with sulfadiazine by mouth had failed.

Infections of the Ear

There are few reports on the streptomycin treatment of infections of the ear. One report includes 8 cases of otitis media, with improvement in 7 and no effect in 1.[202] A child with otitis media and mastoiditis due to *Ps. aeruginosa* failed to respond to streptomycin.[202]

Streptomycin has been used locally in 27 cases of suppurative ear infections that were mainly due to chronic otitis media.[221] Streptomycin preparations containing 1 to 20 mg. per cubic centimeter of physiologic saline solution were instilled four times daily for one to seven weeks. Drainage stopped during treatment and did not recur during follow-up periods of one to four months in about half the cases. In the others the discharge persisted or recurred after temporary improvement. Changes in the bacterial flora were frequent, and streptomycin-resistant strains developed in many of the cases during treatment.

Otitis externa was treated with wicks saturated with streptomycin solutions of 2.5 to 5 mg. per cubic centimeter in 6 cases; 5 patients improved and 1 with insensitive organisms was unimproved.[225] In 3 cases of mastoiditis, 2 patients were improved and 1 unaffected by streptomycin, but all 3 required surgery.[225]

Infections of Skin, Wounds and Bones

Streptomycin solutions, in the form of 2 to 5 mg. per cubic centimeter on wet dressings, were applied directly to sloughing or granulating wounds of 4 patients with burns or avulsions.[74] All improved; granulations became red and healthy, and grafts took well. The bacterial flora, however, did not change, except that the resistance of some of the organisms to streptomycin increased markedly. In 19 patients with infections of the skin, 11 improved and 8 showed no effect from streptomycin given

intramuscularly or, in some cases, topically.[202] Six patients with operative-wound infections also improved.[202] Streptomycin in a base of carbowax and propylene glycol was found helpful in several cases of persistent infections of the skin around the anus.[86]

In Army hospitals 179 patients with wound infections were treated, with improvement in 72, no improvement in 105 and death in 2.[225] Improvement usually coincided with adequate revision of the wounds, and streptomycin was considered useful only as an adjunct to surgery. One patient with pemphigus was unimproved; whereas 1 case each of generalized furunculosis and acneiform ulcerations improved after neither had responded to penicillin.

Topical streptomycin has been considered superior to penicillin in experimental wound infections because of its wider range of activity under such conditions.[184]

Osteomyelitis

Streptomycin may be useful in cases of osteomyelitis in which susceptible gram-negative bacilli predominate, but it seems to be of value mainly as an adjunct to adequate surgery.[74, 254, 255] Improvement has been noted in 11 of 15 reported cases,[74, 202, 254, 255] One fatal case due to widespread infection followed the gradual development of resistance by the causative organism, *A. cloacae*.[254] In some cases, healing continued despite the development of resistant strains, suggesting that the surgery was an important part of the therapy.[255]

Tuberculosis

The most extensive studies on the use of streptomycin in clinical tuberculosis thus far reported are those of Hinshaw and his collaborators.[205, 256] They had previously satisfied themselves that this antibiotic was distinctly superior to the sulfones (Promin, Diasone and Promizole) in the treatment of experimental tuberculosis in guinea pigs.[126, 155, 156] Another series of cases is under close study by Dr. Walsh McDermott at the New York Hospital,[202] and isolated cases of tuberculous meningitis have been reported from other clinics.[70, 84, 257–260] The report of the National Research Council[202] summarized the findings in 87 of these cases. A group of 15 cases was also reported from Army hospitals.[225] A considerable experience is also being accumulated in Veterans Administration hospitals.[261]

Miliary Tuberculosis

The report of the National Research Council[202] mentions 7 patients with miliary tuberculosis, all of whom showed regression of the pulmonary lesions on x-ray examination and reduction of fever and systemic signs of infection during streptomycin therapy. Improvement was usually observed within the first two or three weeks. Three of these patients died, however, and meningitis was observed at autopsy. Of special interest are 2 patients who developed signs of meningitis while receiving intramuscular streptomycin; the meningitis apparently responded after the drug was also given intrathecally. The importance of early diagnosis and persistent treatment with maximum tolerated doses parenterally has been stressed.[205] Clinical, x-ray and histopathologic evidences of healing trends have been observed, but no actual cures are as yet reported.[205]

Tuberculous Meningitis

The results of intensive treatment both intramuscularly and intrathecally for at least four months in this highly fatal disease are somewhat encouraging regarding the possibility of producing arrest of the infection. Parenteral therapy alone appears to be inadequate. The cerebrospinal fluid usually continues to show elevated protein and cell counts, although the values for sugar may become normal after therapy. Serious sequelae, however, have been observed among most of the survivors. The 4 survivors among the 7 patients treated by Hinshaw and his co-workers[205] had received intrathecal therapy, — the 3 patients who died had not, — and all had some form of residual neurologic disturbances; thus, one was blind, probably owing to retrobulbar neuritis, one was deaf, possibly as a result of the toxic effects of the streptomycin, the third had profound disturbances of cerebellar function and some mental retardation, and the fourth had paralysis of one of the ocular muscles. In 9 cases reported by others[70, 84, 225, 257–260] 3 patients recovered, with apparent improvement in the neurologic findings, and the other 6 died.

Pulmonary Tuberculosis

The cases reported were selected chiefly from among those with positive sputums and far advanced or moderately advanced lesions that would be expected to advance under conventional treatment. Streptomycin was given for two to six months in doses of 1 to 3 gm. daily. No progression of the disease was noted clinically or on x-ray study in any of the cases during therapy, and even the fatal cases showed some subjective improvement.[205] X-ray improvement and negative sputums during treatment were noted in two thirds of the cases; a similar proportion of those with cavities showed closure of these cavities. Reactivation occurred a month after the treatment had been discontinued in 6 of a group of 32 cases, in 3 of which the patients were given a second course; 2 then improved, whereas the third had a rapid progression to a fatal outcome associated with a streptomycin-resistant strain of *Mycobacterium tuberculosis*. There were 4 other deaths, all in far advanced cases.[205] In 4 cases treated in Army hospitals, 3 patients were unim-

proved, and 1 with pneumonia was markedly improved.[225]

Only 4 cases of early infiltrative pulmonary tuberculosis treated with streptomycin have been reported.[262] These were all in young children with proved tuberculosis. On a dosage of 1 gm. daily for twenty or thirty days there was clinical and roentgenologic improvement. The patients had remained well during a follow-up period of two or three months.

Streptomycin may have contributed to the recovery of 7 patients treated with radical surgery for pulmonary tuberculosis.[205]

Renal Tuberculosis

Streptomycin was not considered curative in renal tuberculosis, and bacilluria tended to recur in the advanced cases.[205] Six out of 14 patients obtained only temporary subjective relief and 8 had a reduction or disappearance of tubercle bacilli from the urine by direct smear.[202, 225, 263] Only 2, however, had consistently negative guinea-pig tests for prolonged periods. In another group of 7 cases, 2 patients were improved and 5 were unimproved.[225]

Miscellaneous Forms

Six patients with visible ulcerating tuberculous lesions of the upper respiratory tract, trachea and bronchi were treated with streptomycin; all showed healing of the lesions within three to six weeks.[202, 205, 264] Only 1 of 8 patients with tuberculous empyema showed improvement despite intrapleural injections, with or without intramuscular treatment.[202] Cutaneous tuberculous fistulas were treated in 15 cases, in 10 of which the fistula closed during therapy and had remained closed for four to ten months.[205] Prompt healing of a chronic tuberculous sinus in 1 patient occurred with streptomycin therapy.[265] Three patients with tuberculous peritonitis showed clinical improvement.[205] Four of 5 patients with tuberculosis of the bones and joints improved under treatment with streptomycin.[205] Only 1 of 4 patients with lupus vulgaris improved.[205, 225]

Histologic Studies

Pathological changes have been studied in 5 patients who died following treatment for tuberculosis with streptomycin over periods of several weeks or longer.[266] The tuberculous lesions of the spleen, liver and particularly the lungs seemed to be more discrete and less cellular than those seen in untreated cases. Many of the lesions were atrophic, fibrotic and hyalinized and showed a minimum of caseation. Meningeal lesions were absent in some patients in whose cerebrospinal fluid tubercle bacilli had previously been demonstrated.

The consensus regarding the role of streptomycin in the treatment of tuberculosis in human beings is that it exerts a palliative effect by producing some degree of bacteriostasis. The immediate results have been most striking in miliary, meningeal and laryngeal tuberculosis.[202] The disease requires large doses — about 3 gm. daily in adults — for prolonged periods, and treatment should not be undertaken unless adequate amounts of streptomycin are available to permit continuous therapy for at least two to four months. It is generally agreed that streptomycin cannot be regarded as a substitute for present methods of sanatorium and surgical therapy.[205, 267] Further study of the entire problem of streptomycin therapy in tuberculosis is being sponsored by the American Trudeau Society, the medical section of the National Tuberculosis Association.[267]

Tularemia

Streptomycin is particularly efficacious in the treatment of acute tularemia.[202, 203, 207, 225, 227, 240, 268–277] It seems to be equally effective against all the acute forms that have been treated — ulceroglandular, typhoidal and pulmonary. A comparative study of the treatment of tularemia with immune serum, hyperimmune serum and streptomycin indicates that streptomycin is the therapy of choice in desperately ill patients and that only streptomycin or hyperimmune serum reduces the mean duration of the disease to less than two and a half months if treatment is begun later than the second week of the disease.[271]

The report of the Committee on Chemotherapeutics and Other Agents[202] includes 67 cases of all types of tularemia, with recovery in 63. There was pulmonary involvement in 11, and the majority of these patients had previously received sulfonamide and penicillin therapy without effect. The average dose was only about 1.0 gm. daily for a period of seven days.

A series of 11 cases of tularemic pneumonia and 1 case of tularemic pleurisy has been reported in which all the patients showed a prompt clinical response to 0.4 to 1.6 gm. daily for six to fourteen days. Most of them received 0.5 or 0.6 gm. a day for six or seven days. One of the patients died suddenly on the seventh day of treatment, presumably of a massive pulmonary embolus: the temperature had been normal for four days, and the pulmonary lesion had been regressing. *Pasteurella tularensis* disappeared rapidly from the sputum or pleural fluid in all cases. It was believed that healing of the pulmonary lesions and the primary ulcers was accelerated, but clinical recovery occurred even more promptly. Serum agglutinin titers rose in all cases after treatment, and this rise was marked and rapid in some cases. The results were considered to justify a clinical therapeutic trial of streptomycin in doses of 1 to 2 gm. daily in cases of severe pneumonia of undetermined etiology occurring where tularemia is endemic.[277]

Three patients were treated with streptomycin because of the persistence of easy fatigability, malaise and intermittent fever several months after an episode of acute tularemia.[275] These patients, who were possibly suffering from chronic tularemic infection, showed no improvement in their symptoms and signs.

Brucellosis

Streptomycin has not proved to be of great value in the treatment of brucellosis. Reports of 77 cases, mostly acute infections, are available.[62, 84, 202, 203, 218, 248, 278–280] Blood cultures were usually negative during treatment, but bacteremia often recurred after therapy had been stopped, and in 1 case persisted during and after the treatment.[203] The effect on the relapse rate remains to be determined, but 2 cases have been reported in which evidence of chronic brucellosis persisted during a follow-up period of one and a half to two years.[281] The development of a markedly resistant strain of *Br. abortus* occurred during streptomycin treatment in one case of chronic brucellosis.[62] The possibility of better effects from a combination of sulfadiazine and streptomycin is suggested from results in 2 cases.[279]

Miscellaneous Infections

Streptomycin was used in a group of 9 cases of chronic urethritis due to *Neisseria gonorrhoeae* that were clinically resistant to sulfonamide and penicillin therapy[282]; 7 cases cleared promptly after a short course of streptomycin consisting of six intramuscular injections of 0.5 gm. each. One of the patients, who had prostatic involvement, improved clinically but was not cured; in another, who had chronic epididymitis, smears of the urethral discharge became negative, but the epididymitis did not clear. In another group of 4 previously untreated cases, streptomycin produced a favorable response.[283] Streptomycin is probably indicated for the occasional cases of gonorrhea that prove resistant to sulfonamides and penicillin.

No published reports are available on the use of streptomycin in clinical cases of pertussis. Bradford[212] found that streptomycin in nose drops (10 mg. per cubic centimeter, five drops in each nostril every three hours) or used as an aerosol for three days was effective in eliminating *H. pertussis* from throat cultures. After intramuscular injections negative cultures were not obtained so rapidly as after the local applications.

Malleomyces mallei was eliminated by streptomycin treatment from the skin ulcers of a patient with osseous tuberculosis and secondary glanders.[203]

Streptomycin is somewhat effective in experimental spirochetal infections in animals, as noted above in Part I. In a clinical study streptomycin was given in small doses over a ten-day period to 3 patients with early syphilis and to 1 with a gummatous lesion; all improved but later relapsed.[240]

No reports have been found on the use of streptomycin in human viral infections. In 2 patients with typhus fever streptomycin had no effect.[202]

One patient with acute pulmonary moniliasis,[74] 1 with blastomycosis of the skin and 1 with a *Cryptococcus hominis* meningitis were treated with streptomycin without effect.[225] No reports are available on the use of the antifungal antibiotic derived from cultures of *Streptomyces griseus* in the treatment of human cases.[7, 8]

A case of human amebic hepatitis was treated ineffectively with streptomycin.[202]

Diseases of Uncertain Etiology

Streptomycin has been used in 29 cases of ulcerative colitis,[86, 202, 225, 284, 285] with dramatic improvement in only 2 cases,[284, 285] temporary improvement in 6 and failure to arrest the disease in the remaining 21. In some acute exacerbations the drug sometimes lowered the temperature and seemed to avert a fatal outcome.[86] No beneficial effect from streptomycin was observed in 6 cases of rheumatoid arthritis,[202] 1 case of infectious mononucleosis,[202] 1 case of relapsing febrile panniculitis (Weber–Christian's syndrome),[203] 1 case of Hodgkin's disease[225] and 1 case of Reiter's syndrome.[202] Six patients with nonspecific urethritis were treated with streptomycin; 2 were improved, and the remainder were unimproved after several days of therapy.[282] Dienes and Kane[286] found streptomycin to be of value in some cases of genitourinary infections in which cultures yielded pleuropneumonia-like organisms. They also observed suggestive effects on the course of the disease in cases of Reiter's syndrome. In 13 infants with epidemic diarrhea of undetermined etiology treated with oral streptomycin alone, 10 improved, and 3 died; in at least 4 of these cases survival was attributed to the streptomycin.[225] The drug seemed beneficial in a case of pylethrombophlebitis.[287]

Toxic Effects

Although most patients tolerated streptomycin quite well, the drug is not nearly so free of untoward effects as penicillin. Both local and constitutional reactions are frequent, but none have been reported thus far following ingestion, inhalation or local applications to skin and wounds.

Local Reactions

Pain, tenderness and induration at the site of intramuscular injections are quite frequent and are often accompanied by local redness and heat.[202] These manifestations may be more frequent and severer with subcutaneous injections. The incorporation of procaine hydrochloride may lessen the discomfort that follows within a few minutes after the injection, but the immediate discomfort may

be minimized if the volume of injected material is kept to a minimum. The use of "pure" crystalline streptomycin sulfate is said to produce only minimal discomfort at the site of injection.[202]

In the treatment of meningitis in human beings, intrathecal injections of streptomycin have been attended by few untoward effects, in contrast to the reactions noted in experimental animals.[185, 186] Severe reactions were observed in 5 patients immediately or within nine hours after the first intrathecal or intraventricular injection of 2500 to 100,000 units of streptomycin in concentrations of 10,000 to 20,000 units per cubic centimeter.[206] These reactions were characterized by coma and changes in pulse, temperature and respiration. Death from respiratory failure occurred in 2 cases. Since all patients had meningitis, the deaths were not necessarily related to the injections of streptomycin. Early and probably impure lots were used in these cases. Streptomycin given by these routes to many patients with meningitis has been followed by much benefit, without these alarming reactions.[80, 81, 119, 202, 204]

An increase in meningeal signs or pleocytosis in the cerebrospinal fluid, or both, has been observed.[72, 81, 119, 206] Fever and pleocytosis may persist in patients recovering from meningitis who are receiving intrathecal streptomycin, but these signs promptly subside when the intrathecal injections are stopped.[81] Even in subjects without meningitis the cerebrospinal fluid may contain 180 to 1500 white cells per cubic millimeter, mostly polymorphonuclears, twenty-four hours after the intrathecal injection of 10 to 20 mg. of streptomycin.[72] These mild reactions should not discourage the use of streptomycin by this route, since the drug is such an important part of the treatment of meningitis.

Constitutional Reactions

Headache, flushing of the skin, nausea, vomiting, a fall in blood pressure and occasionally convulsions were observed immediately following injection of some of the earlier lots of streptomycin.[69, 71, 85, 202, 288] This type of reaction, which is due to a histamine-like impurity in the streptomycin,[37, 289] may be avoided by the use of benadryl,[188] and probably with pyribenzamine, although the use of the latter has not been reported. Two deaths have been ascribed to this type of reaction following injections of streptomycin.[290] Recent lots of streptomycin are relatively free from the histamine-like substance.[37, 202]

Skin eruptions and fever may appear, together or separately, usually between the third and tenth days of streptomycin treatment. The skin lesions may be erythematous, urticarial, maculopapular or hemorrhagic.* Such reactions may recur on subsequent administration. Eosinophilia has been noted with and without the skin rash. Myalgias and arthralgias were noted, especially with some of the earlier batches of streptomycin.[71, 72, 85, 288] Streptomycin should usually be discontinued if these reactions appear.[202]

Probably the most striking untoward effect of streptomycin has been the disturbance of function of the eighth cranial nerve, apparently without relation to the injection of streptomycin into the central nervous system. This effect has been noted with both early and recent batches of streptomycin, suggesting that the effect is not due to an impurity but perhaps represents a selective neurotoxic action of the drug.[37, 289] The incidence of this type of reaction in human beings varies. Only 2 cases of vestibular disturbance were recognized among 706 patients treated in Army hospitals.[225] Absence of vestibular response was noted in 3 of another series of 81 streptomycin-treated patients after average doses of 0.5 gm. intramuscularly every four hours for a total of 10 to 50 gm.[181] These 3 had complained of dizziness during treatment. The patients treated ranged in age from nineteen to fifty-one years, and those with known ear disease or meningitis were excluded. An additional patient in this group manifested a severe loss of hearing two weeks after treatment but later improved.

Symptoms of eighth-nerve difficulty were reported in 23 cases among those treated at the Mayo Clinic.[180] No patients complained of true objective or subjective vertigo, but they experienced dizziness, light-headedness or giddiness; these symptoms were first noted on change of position. Most of the patients had a positive Romberg test; the imbalance varied from a gentle swaying in all directions to falling in any direction. The patients usually could not walk unassisted. Spontaneous nystagmus, which was noted in 1 patient on change of position, disappeared forty-eight hours after the streptomycin had been stopped. Five of the 23 patients had some loss of hearing; 4 of these 5, however, had tuberculous meningitis. Loss of hearing was noted with daily doses of 3 to 10 gm., but not with 1 or 2 gm. Tinnitus preceded the loss of hearing in all 5 cases. In 3 cases the hearing improved when the streptomycin was stopped or the dose decreased, and in 1 case, deafness recurred when streptomycin was reinstituted. It was therefore believed that streptomycin affected the cochlear apparatus and produced temporary deafness. The loss of vestibular response as judged by caloric and rotation tests has persisted in most of the patients. The patients compensate for this defect, however, by other postural mechanisms so that the symptoms usually persist only for one to three months.[180, 202]

Davenport[261] reported 90 per cent incidence of vestibular changes in patients treated with streptomycin for tuberculosis, and varying degrees of deafness resulted in a small number of cases.

Toxic effects of streptomycin on the kidneys and livers of experimental animals were described in Part I. No effects on liver or kidney function were noted after single doses of 600 mg. intravenously in

*Davenport[261] noted the occurrence of exfoliative dermatitis in 1 case.

6 subjects, and no latent toxic effects were observed in 100 patients given an average total dose of 12.5 gm. over a ten-day period.[69] Abnormal urinary findings and urinary retention were noted with some early and impure lots of streptomycin.[183, 186, 288] Hyaline and granular casts were found in the urine of 9 of 10 patients receiving crystalline streptomycin, particularly when the urine was acid.[202] There was no evidence of renal impairment,[69, 71, 288] as judged by urea-clearance tests, blood nonprotein nitrogen determinations and concentration-dilution tests. Effects of streptomycin on the kidneys, as manifested by proteinuria, cylindruria, hematuria, and occasionally azotemia, have been noted in another group of patients, but these effects disappeared on withdrawal of the drug.[225] Two cases of acute nephritis have been noted in patients with typhoid fever under treatment with streptomycin.[213, 291] The role of streptomycin in these cases is not clear.

A diffuse fatty degeneration of the liver was noted at autopsy of a patient who had received streptomycin therapy for miliary tuberculosis, peritonitis and meningitis, but the cause of the liver changes was not clear.[186] No evidence of impairment of the hematopoietic system has been reported by most observers.[69, 70, 71, 186, 288] Thrombocytopenic purpura occurred during streptomycin treatment of a case of brucellosis and cleared promptly when the antibiotic was withdrawn.[291]

Development of Bacterial Resistance during Treatment

The appearance of resistant strains of bacteria has been noted during streptomycin treatment of urinary-tract infections,[31, 50, 74, 110, 194, 202, 213, 224,–226, 240] respiratory-tract infections,[82, 192] meningitis,[80, 119, 203] otitis,[221] enteric infections (cholera),[124] biliary-tract infections,[110, 240] osteomyelitis[74, 254] and infections of the skin and wounds.[74] A wide variety of bacteria that have been observed to acquire resistance to streptomycin in man during therapy include: *A. aerogenes*,[31, 50, 110, 194, 224] *A. cloacae*,[25] *Esch. coli*,[50, 213, 214, 240] a paracolon bacillus,[50] *Ps. aeruginosa*,[31, 50, 110, 255] *Pr. vulgaris* (*B. proteus*),[194, 226] *K. pneumoniae*,[50, 82] *H. influenzae*,[80, 82,–119, 203] *V. comma*,[124] *Myco. tuberculosis* var. *hominis*,[192, 198, 205] *Staph. aureus* and *Staph. albus*,[110] alpha-hemolytic and beta-hemolytic streptococci,[110] *Str. faecalis*,[214, 226] *Br. abortus*[62] and possibly diphtheroids.[110]

Theories on the development of resistance were discussed in Part I. Regarding the occurrence of this phenomenon clinically, two possible explanations have been offered: either the original pretreatment bacterial population consists of both resistant and susceptible organisms and exposure to streptomycin eliminates the sensitive strains and allows the resistant ones to flourish or the naturally sensitive strains become adapted to the antibiotic in some manner so that they can multiply in its presence. Naturally resistant strains, including *Esch. coli*, *Pr. vulgaris*, *Ps. aeruginosa*, alpha-hemolytic streptococci and diphtheroids, have been noted,[52, 99, 110] The usual methods for determining bacterial sensitivity are such that small numbers of naturally resistant organisms may easily be missed. The occurrence or appearance of resistant strains in man during streptomycin therapy is important because it may seriously interfere with the efficacy of the treatment.

Alkalinization of the urine during streptomycin therapy[85] may offer a means of limiting the development of resistant strains of organisms in some cases of urinary-tract infection. The use of large initial doses of streptomycin in an attempt to avoid exposure of the organisms to subinhibitory concentrations of the drug seems logical and has been suggested.[202, 214–216, 228, 289] Yet even when large doses of streptomycin were given initially, resistant strains of bacteria sometimes developed, particularly when the reaction of the urine was acid.[50]

In cases of tuberculosis, resistant strains may not become apparent until after several weeks or months of treatment. Tubercle bacilli obtained from such cases are equally resistant when cultured directly from sputum, urine or gastric aspirations, from such cultures after storage in a refrigerator or when the cultures are made from infected organs of guinea pigs inoculated ten or more weeks previously with material from the patient and when subsequently maintained on glycerine egg agar for several weeks.[198] The implications of these observations regarding the possibility of streptomycin therapy in cases of cross-infection or laboratory infection with such strains are obvious.

Just how long resistant strains may persist in the patient once they have appeared during therapy is not known. In some patients treated for chronic urinary-tract infections, such resistant strains were demonstrated for several months[85] and in 1 case, for as long as eleven months.[117]

Summary

Streptomycin has proved most effective in acute tularemia and in cases of meningitis due to gram-negative bacilli, especially *Haemophilus influenzae*. It is useful in most gram-negative bacillus infections, particularly those of the urinary and respiratory tracts. The results in some forms of tuberculosis are encouraging, and it is at present the best available chemotherapeutic agent for tuberculous infections. Typhoid fever, Salmonella infections and brucellosis have not responded favorably. It may be useful as a second line of defense in some cases of coccal infections that prove insensitive to the sulfonamides and penicillin or develop fastness to these agents.

The greatest limitation to the clinical usefulness of streptomycin is the readiness with which most organisms develop resistance to it.

Streptomycin is relatively nontoxic. The most serious untoward effect that has been noted is a disturbance in vestibular function. This effect has been observed mainly following the use of large amounts of the drug over prolonged periods.

Streptomycin is a valuable addition to the group of agents that are used for the definitive treatment of infectious diseases, particularly since it is effective in some infections that are influenced little, if at all, by other available agents.

References

202. Committee on Chemotherapeutics and Other Agents, National Research Council. Streptomycin in treatment of infections: report of one thousand cases. *J. A. M. A.* **132**:4-11 and 70-76, 1946.
203. Morgan, H. J., and Hunt, J. S. Streptomycin in clinical practice: review and case reports. *Am. Practitioner* **1**:73-86, 1946.
204. Weinstein, L. Treatment of meningitis due to *Haemophilus influenzae* with streptomycin: report of nine cases. *New Eng. J. Med.* **235**:101-111, 1946.
205. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. Treatment of tuberculosis with streptomycin: summary of observation on one hundred cases. *J. A. M. A.* **132**:778-782, 1946.
206. Cairns, M., Duthie, E. S., and Smith, H. V. Intrathecal streptomycin in meningitis: clinical trial in tuberculous, coliform, and other infections. *Lancet* **2**:153-155, 1946.
207. Atwell, R. J., and Smith, D. T. Primary tularemia pneumonia treated with streptomycin: report of two cases. *South. M. J.* **39**: 858-860, 1946.
208. Olsen, A. M. Streptomycin aerosol in treatment of chronic bronchiectasis: preliminary report. *Proc. Staff. Meet., Mayo Clin.* **21**: 53, 1946.
209. Durant, T. M., Sokalchuk, A. J., Norris, C. M., and Brown, C. L. Streptomycin therapy in Hemophilus influenzae pulmonary infections. *J. A. M. A.* **131**:194-196, 1946.
210. Owens, W. C. Streptomycin treatment of corneal abscess caused by Escherichia coli. *Am. J. Ophth.* **29**:1007-1009, 1946.
211. Alberstadt, N. F., and Price, A. H. Corneal ulcer treated with streptomycin. *Am. J. Ophth.* **29**:1106-1111, 1946.
212. Bradford, W. L. Personal communication.
213. Keefer, C. S., Weinstein, L., and Hewitt, W. L. Clinical experience with streptomycin: study of 50 cases. *Tr. A. Am. Physicians* **59**: 206-219, 1946.
214. Adcock, J. D., and Plumb, R. T. Streptomycin for urinary tract infections. *J. A. M. A.* **133**:579-584, 1947.
215. Potter, J. E. Discussion of Adcock and Plumb.[214]
216. Hirshfeld, J. W. Discussion of Adcock and Plumb.[214]
217. Reimann, H. Discussion of Keefer, Weinstein, and Hewitt.[213]
218. Zantiny, W. G., and Carlson, H. J. Experiences with streptomycin: effectiveness in infections of infants and children. *Clinics* **5**:635-645, 1946.
219. Hoyne, A. L., Brown, R. H., and Drucker, A. P. Influenzal meningitis treated with streptomycin: report of three cases with recoveries. *Arch. Pediat.* **63**:559-566, 1946.
220. Shields, W. P. Meningitis due to *Escherichia coli*: streptomycin therapy. *J. A. M. A.* **132**:514, 1946.
221. Harris, H. W., and Finland, M. Experiences with streptomycin therapy. *North Carolina M. J.* (in press).
222. Jacobi, H. G. Streptomycin in treatment of case of persistent urinary infection. *New York State J. Med.* **46**:883-890, 1946.
223. Blackstone, B. B. G., Sommerness, M. D., and Scott, E. G. Treatment of obstinate case of aerobacter bacilluria with streptomycin. *Delaware State M. J.* **18**:101-104, 1946.
224. Bondi, A., Jr., Ottenberg, D., Dietz, C. C., and Brown, C. L. Streptomycin therapy in infections of urinary tract: failure because of development of resistance. *J. A. M. A.* **132**:634, 1946.
225. DeBakey, M. E., and Pulaski, E. J. Analysis of experience with streptomycin in United States Army hospitals: preliminary report. *Surgery* **20**:749-760, 1946.
226. Raines, S. L. Present status of streptomycin therapy. *J. Urol.* **57**: 79-83, 1947.
227. Aikawa, J. K., Gillikin, C. M., Herndon, E. G., Jr., and Harrell, G. T. Simple laboratory aids for control of streptomycin therapy in general practice. *South. M. J.* **40**:141-153, 1947.
228. Pool, T. L., and Cook, E. N. Present concepts of treatment of infections of urinary tract. *J. A. M. A.* **133**:584-587, 1947.
229. Albright, F. Personal communication.
230. Kane, L., and Foley, G. E. Personal communication.
231. Butler, L. J., Yow, M. D., and Reinhart, J. B. Meningitis due to Hemophilus influenzae: report of case treated with sulfadiazine, streptomycin, and antiserum, with recovery. *North Carolina M. J.* **7**:8-12, 1946.
232. Nussbaum, S., Goodman, S., Robinson, C., and Ray, L. Influenzal meningitis: report of three cases treated with streptomycin and sulfadiazine. *J. Pediat.* **29**:14-19, 1946.
233. Alexander, A. J. Meningitis due to Escherichia coli treated with streptomycin. *J. A. M. A.* **131**:663-665, 1946.
234. Tartakoff, S., Grynbaum, B., and LeCompte, P. M. Friedländer-bacillus meningitis treated with streptomycin. *New Eng. J. Med.* **235**:681-683, 1946.
235. Barnes, M. Salmonella meningitis: report of case treated with streptomycin. *Bull. Charlotte Memorial Hosp.* **2**:44-47, 1946.
236. Bishop, C. A., and Rasmussen, R. F. Klebsiella pneumonia treated with streptomycin. *J. A. M. A.* **131**:821, 1946.
237. Learner, N., and Minnich, W. R. Friedländer pneumonia treated with streptomycin: report of case with prompt recovery. *Ann. Int. Med.* **25**:516-520, 1946.
238. Geier, F. M. Case of Friedländer's bacillus pneumonia treated with streptomycin. *Permanente Foundation M. Bull.* **4**:159-163, 1946.
239. *A Textbook of Medicine by American Authors.* Edited by R. L. Cecil. 1566 pp. Philadelphia: W. B. Saunders Company, 1943. P. 315.
240. Nichols, D. R., and Herrell, W. E. Streptomycin: its clinical uses and limitations. *J. A. M. A.* **132**:200-206, 1946.
241. Segal, M. S., and Ryder, C. M. Penicillin inhalation therapy. *New Eng. J. Med.* **236**:132-138, 1947.
242. Barach, A. L., Garthwaite, B., Soroka, M., and Anderson, F. F. Apparatus for introduction of penicillin aerosol into nasal accessory sinuses with case report of patient with chronic sinusitis. *Ann. Int. Med.* **24**:97-103, 1946.
243. Herrell, W. E., and Nichols, D. R. Clinical use of streptomycin; study of forty-five cases. *Proc. Staff Meet., Mayo Clin.* **20**:449-462, 1945.
244. Hunter, T. H., and Duane, R. B., Jr. Subacute bacterial endocarditis due to gram negative organisms. *J. A. M. A.* **132**:209-211, 1946.
245. Cady, J. B., and Allen, W. H. Case of streptococcus fecalis septicemia treated unsuccessfully with streptomycin. *Guthrie Clin. Bull.* **16**:31-33, 1946.
246. Cady, J. B., and Hunter, A. L. Streptococcus fecalis septicemia: concluding report of case. *Guthrie Clin. Bull.* **16**:90-93, 1947.
247. Goldbloom, A. A., Dumanis, A. A., and Seidmon, E. E. P. Streptomycin in typhoid fever: review of current literature and usage. *New York State J. Med.* **46**:1936-1939, 1946.
248. Pulaski, E. J., and Amspacher, W. H. Streptomycin therapy in typhoid infections. *Bull. U. S. Army M. Dept.* **7**:101-107, 1947.
249. Grossman, L. A., and Hunt, J. S. Typhoid fever: treatment failure with streptomycin. *Am. Practitioner* **1**:45, 1946.
250. Flippin, H. F. Cited by Waksman and Schatz.[3]
251. Muellner, S. R., and Rutenberg, A. Use of streptomycin in colon bacillus peritonitis: report of case. *New Eng. J. Med.* **235**:327, 1946.
252. Crile, G., Jr. Peritonitis of appendiceal origin treated with massive doses of penicillin: report of 50 cases. *Surg., Gynec. & Obst.* **83**: 150-162, 1946.
253. Duke-Elder, W. S. Diseases of cornea. In *Textbook of Ophthalmology.* Vol. 2. 2094 pp. St. Louis: C. V. Mosby Company, 1944. P. 1915.
254. Edwards, M. W., and Kirk, G. D. Development of resistance to streptomycin by *Aerobacter cloacae*. *Am. J. Clin. Path.* **16**:527-529, 1946.
255. Lamphier, T. A., and Cashman, C. Treatment of chronic osteomyelitis with streptomycin: preliminary report. *New Eng. J. Med.* **236**:318-321, 1947.
256. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. Streptomycin in treatment of clinical tuberculosis. *Am. Rev. Tuberc.* **54**: 191-203, 1946.
257. Cooke, R. E., Dunphy, D. L., and Blake, F. G. Streptomycin in tuberculous meningitis: report of its use in one-year-old infant. *Yale J. Biol. & Med.* **18**:221-226, 1946.
258. Thompson, J. L., and Wagenheim, H. H. Use of streptomycin in acute miliary tuberculosis: report of case. *M. Ann. District of Columbia* **15**:265-270, 1946.
259. Bornstein, P. K. Streptomycin in miliary tuberculosis with tuberculous meningitis: case report with autopsy findings. *Quart. Bull. Sea View Hosp.* **8**:219-227, 1946.
260. Krafchik, L. L. Tuberculous meningitis treated with streptomycin. *J. A. M. A.* **132**:375, 1946.
261. Davenport, L. F. Streptomycin in pulmonary tuberculosis. *Bull. New Eng. Med. Center* **9**:83-85, 1947.
262. Sanford, H. N., and O'Brien, D. E. Streptomycin in pulmonary tuberculosis in childhood: results in four children. *J. A. M. A.* **133**: 691-693, 1947.
263. Cook, E. N., Greene, L. F., and Hinshaw, H. C. Streptomycin in treatment of tuberculosis of urinary tract. *Proc. Staff Meet., Mayo Clin.* **21**:277-280, 1946.
264. Figi, F. A., Hinshaw, H. C., and Feldman, W. H. Treatment of tuberculosis of larynx with streptomycin: report of case. *Proc. Staff Meet., Mayo Clin.* **21**:127-130, 1946.
265. Morgan, C., and Bosworth, D. M. Transpleural rupture of tuberculous spinal abscess treated successfully by streptomycin: report of case. *J. Bone & Joint Surg.* **28**:864-868, 1946.
266. Baggenstoss, A. H., Feldman, W. H., and Hinshaw, H. C. Effect of streptomycin on histopathology of human tuberculosis. *Am. J. Path.* **22**:641, 1946. Streptomycin in miliary tuberculosis: its effect on pathological lesions of generalized miliary tuberculosis in human beings. *Am. Rev. Tuberc.* **60**:54-76, 1947.
267. Medical News. Distribution of streptomycin. *J. A. M. A.* **132**:531, 1946.
268. Foshay, L., and Pasternack, A. B. Streptomycin treatment of tularemia. *J. A. M. A.* **130**:393-398, 1946.
269. Abel, O., Jr. Use of streptomycin in tularemia. *J. Missouri M. A.* **43**:167-169, 1946.
270. Heather, A. J., and Scott, E. G. Tularemia: case treated with streptomycin. *Delaware State M. J.* **18**:148-150, 1946.
271. Foshay, L. Comparative study of treatment of tularemia with immune serum, hyperimmune serum and streptomycin. *Am. J. Med.* **1**:180-188, 1946.
272. Cohen, R. B., and Lasser, R. Primary tularemic pneumonia treated with streptomycin. *J. A. M. A.* **131**:1126, 1946.
273. Peterson, R. L., and Parker, R. R. Tularemic pneumonia: treatment with streptomycin. *Pub. Health Rep.* **61**:1231-1234, 1946.

274. Gordon, A. M. Streptomycin in tularemia. *J. A. M. A.* **132**:21, 1946.
275. Howe, C., Coriell, L. L., Bookwalter, H. L., and Ellingson, H. V. Streptomycin treatment in tularemia. *J. A. M. A.* **132**:195-200, 1946.
276. Hartnett, W. G., and Mollica, S. G. Tularemia: treatment of case with streptomycin. *South. M. J.* **39**:774-777, 1946.
277. Hunt, J. S. Pleuropulmonary tularemia: observations on 12 cases treated with streptomycin. *Ann. Int. Med.* **26**:263-276, 1947.
278. Goelz, J. R. Treatment of undulant fever with streptomycin. *Wisconsin M. J.* **45**:496, 1946.
279. Pulaski, E. J., and Amspacher, W. H. Streptomycin therapy in brucellosis. *Bull. U. S. Army Med. Dept.* **7**:221-225, 1947.
280. Howe, C., Miller, E. S., Kelly, E. H., Bookwalter, H. L., and Ellingson, H. V. Acute brucellosis among laboratory workers. *New Eng. J. Med.* **236**:741-747, 1947.
281. Howe, C. Personal communication.
282. Pulaski, E. J. Streptomycin therapy of penicillin-resistant and sulfonamide-resistant specific and nonspecific urethritis. *J. Ven. Dis. Inform.* **28**:1-6, 1947.
283. Putnam, L. E., Herwick, R. P., Taggart, S. R., and Chinn, B. D. Treatment of gonorrhea with streptomycin: preliminary report with cure of four cases. *M. Ann. District of Columbia* **16**:14 and 55, 1947.
284. Kirschner, B. Acute fulminating ulcerative colitis: treatment with streptomycin. *New York State J. Med.* **46**:525, 1946.
285. Lieberman, W. Streptomycin treatment of intractable ulcerative colitis. *New York State J. Med.* **46**:2178, 1946.
286. Dienes, L. L., and Kane, L. W. Personal communication.
287. Wishart, J. H., and Peterson, L. J. Streptomycin therapy in pylethrombophlebitis. *J. A. M. A.* **133**:539-541, 1947.
288. Hettig, R. A., and Adcock, J. D. Studies on toxicity of streptomycin for man: preliminary report. *Science* **103**:355-357, 1946.
289. Molitor, H. Bacterial chemotherapy. *Federation Proc.* **5**:304-312, 1946.
290. Editorial. Streptomycin. *J. A. M. A.* **130**:939, 1946.
291. Sturgis, C. C. Discussion of Keefer, Weinstein, and Hewitt.[318]

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33201

PRESENTATION OF CASE

First admission. A fifty-six-year-old housewife entered the hospital complaining of abdominal pain and vomiting.

The patient had been in excellent health until two years previously, when she first began to have periodic bouts of nausea and vomiting accompanied by a dull pain in the left upper quadrant. At first the attacks occurred every four or five weeks and lasted for one day. The vomitus was composed of stomach contents with no blood or bile. There was no particular relation to the intake or type of food. During the intervals between attacks she felt well, and the appetite remained normal. After several months, however, she noticed some weight loss. The attacks increased in frequency and severity so that she was admitted to another hospital for study, where a gastrointestinal and a gall-bladder series, as well as a barium enema, were negative. A diagnosis of anemia was made, and liver injections were given for a few months. Nevertheless, she remained unimproved and was forced to eliminate many foods from the diet in an effort to control the pain and vomiting. A "yellow color" developed eighteen months before admission but cleared slowly while iron and weekly injections of liver extract were being given. Then followed a period during which the vomiting and pain subsided, although the patient continued to lose weight. During the following year the attacks recurred, and many studies, including x-ray films, were done, none of which revealed any abnormality other than anemia. Six months prior to admission the skin became "brownish" for a few weeks. At that time the systolic blood pressure was 86. She was given "injections" and ten salt tablets daily, but after five weeks she became extremely edematous and the treatment was stopped. The attacks of pain grew more frequent and at the time of admission were of daily occurrence. She had limited the food in amount and to soft solids and fluids. Most of the attacks of pain, which were described as dull and nagging, came on after meals, arose in the left upper quadrant and radiated across the abdomen to the right. Although the patient often became extremely hungry, she could eat only a few mouthfuls of food and on several occasions "fainted from hunger." The weight had fallen from 175 to 113 pounds, and the nausea and vomiting had become infrequent. She had gradually become constipated during the second year of the illness so that she required a laxative almost daily. There had been no tarry stools.

Physical examination revealed a well developed but pale and emaciated woman in no acute distress. The skin was dry, with poor turgor. Examination of the heart and lungs was negative. There was considerable spasm of the abdominal wall, with an irregular area of marked tenderness immediately to the left of the umbilicus. No masses were palpated. Pelvic examination was negative.

The temperature was 99.4°F., the pulse 86, and the respirations 20. The blood pressure was 88 systolic, 48 diastolic.

X-ray examination of the chest, as well as an intravenous pyelogram, a Graham test and examinations with a barium meal and enema were negative.

Examination of the blood showed a red-cell count of 2,820,000, with a hemoglobin of 4.6 gm., a hematocrit of 20 and a cell volume of 71 cu. microns. A blood smear revealed a marked achromia with some variation in size and shape of the cells. A fragility test was negative. The reticulocyte count was 1.2 per cent, and the white-cell count 13,000, with 80 per cent neutrophils. The urine showed a specific gravity of 1.008, a ++ test for albumin and no sugar; Bence-Jones protein was absent. Several

stools were brown and guaiac negative. The nonprotein nitrogen was 25 mg., the protein 6.8 gm. and the sugar 107 mg. per 100 cc. Gastric analysis showed free hydrochloric acid.

One examiner believed that he felt an irregular mass to the left of the umbilicus and suggested peritoneoscopy. This was done on the tenth hospital day. No masses were visible anywhere in the peritoneal cavity or in the pelvis. The uterus and ovaries were not abnormal. The liver appeared normal and extended three or four fingerbreadths below the costal margin. A liver biopsy was taken during this procedure, and microscopical examination showed no abnormality. The patient was discharged on the eighteenth hospital day.

Final admission (two months later). During the following two months the symptoms continued essentially unchanged. The patient remained on a bland diet, taking iron and vitamins.

X-ray examination showed the stomach to be somewhat dilated, with increased peristalsis. The barium passed readily through the pylorus into the first and second portions of the duodenum, where there was some dilatation. In spite of the increased peristalsis there was a marked delay at this point. There was regurgitation from the duodenum back into the stomach, and only a small quantity of barium passed around the duodenal loop during fluoroscopic examination. Two hours later most of the barium was still in the stomach and duodenum, and only a small quantity had reached the lower jejunum. Six hours after fluoroscopy there was little change. Further examination showed an area of ulceration, 3.5 cm. in diameter, in the upper jejunum. The lumen was irregularly dilated. A number of loops appeared to be adherent, and a mass corresponding to the lesion in the bowel was palpated.

Three transfusions were given, and an operation was performed.

Differential Diagnosis

Dr. Bernard M. Jacobson: This is undoubtedly a case of small-bowel obstruction probably extending over a period of two years. Since I am on the medical service, I am indeed flattered to be presented with such a case. I shall try to uphold the honor of that service in making the diagnosis. I am sure, however, that there are several points about the diagnosis that I shall miss entirely.

The record states that the patient had anemia eighteen months before the first admission. Although she received liver injections for a few months, I believe that the later evidence is sufficient to rule out a liver-deficiency anemia. Certainly, the appearance of the blood is not that of pernicious anemia. The presence of free hydrochloric acid is additional evidence against pernicious anemia as is the fact that a course of liver injections gave no improvement.

A yellow color developed and cleared slowly. I have no idea what this was. It may have been due to a common-duct obstruction, which I do not believe has any relation to the present illness. We are reminded on several occasions that she continued to lose weight despite a fair appetite and despite the subsidence of vomiting and pain. One begins to wonder about malabsorption of food or food products due to diffuse small-bowel disease of some sort. We are told that six months before admission, the systolic blood pressure was 86, that the skin was brownish and that some sort of injections and ten salt tablets daily were given. On the basis of these data it is difficult to make a diagnosis of Addison's disease. The record contains no reference to pigmentation of the skin or mucous membranes and no statement regarding chemical investigation of the electrolytes; there is also no later mention of treatment for Addison's disease. The fact that the patient became edematous indicates overdosage of desoxycorticosterone acetate. During the course, no note is made of the passage of a Miller–Abbott tube for diagnostic purposes in conjunction with the x-ray studies. One wonders why that procedure was not done at the time of the first admission, in view of a history suggestive of small-bowel obstruction. Was a Miller–Abbott tube passed?

Dr. Tracy B. Mallory: No.

Dr. Jacobson: The blood studies indicate a moderately severe hypochromic microcytic anemia. This anemia was the nondescript type that is observed in a large variety of conditions. The normal fragility test and reticulocyte count and the lack of icterus are evidence against the presence of hemolytic anemia, and the normal reticulocyte count is also against the presence of a recent severe intestinal hemorrhage. On the other hand, long-continued oozing of blood can occur in small amounts without a high reticulocyte count as evidence of regeneration in the bone marrow. The figures do not suggest a primary blood dyscrasia, such as leukemia or aplastic anemia. I might add that I do not believe I shall ever be able to explain the anemia properly. I have seen several patients with tumor of the small or large bowel in whom there was no history of frank bleeding, with guaiac-negative stools, and in whom a similar anemia was fairly resistant to treatment. I do not believe that we can rule out occasional slow oozing in this patient, and yet we have no evidence for it. The serum protein of 6.8 gm. per 100 cc. is rather high for a person with severe anemia, and assuming that she was not dehydrated when the blood was taken, I wonder if we are dealing with one of the several conditions that cause hyperproteinemia. There is certainly no evidence of the most frequent condition that occurs with anemia — namely, myeloma. On the

other hand, it must be remembered that a small proportion of other types of lesions, such as granulomas, do show high serum proteins. It is interesting that peritoneoscopy at the first admission revealed no masses in the abdomen. Peritoneoscopy was informative certainly in that the liver biopsy ruled out amyloid disease, which is one of the conditions that the record suggests.

May we see the x-ray films taken at the time of the final admission?

DR. STANLEY M. WYMAN: The first film was taken at the first admission and shows a normal-appearing stomach, duodenal cap and duodenal loop. No abnormal masses can be seen. A review of the films of the first admission suggests some irregularity in the region of the small intestine. The film taken during the second admission shows the irregularity described somewhat better, and it appears to be a filling defect of the lumen of the small intestine. The exact contour cannot be well outlined. The mucosal pattern in this region is no longer present.

DR. WALTER BAUER: You have no hesitancy in saying that the mucosa is ulcerated?

DR. WYMAN: I believe that it is.

DR. JACOBSON: Is there anything that looks like pipestem infiltration in the small bowel?

DR. WYMAN: A sclerosing process? I do not believe so.

DR. JACOBSON: The ulcerating process and the obvious x-ray evidence of obstruction in the upper part of the small intestine compel me to consider the differential diagnosis of obstruction. Inasmuch as we are told that there was an area of ulceration in the mucosa, the differential diagnosis becomes considerably limited. As I look back over the case, the period of two years with similar symptoms makes it seem logical to assume that this was a tumor, either benign or possibly mildly malignant, that started either in the lymphoid patches or the muscularis and gradually became larger, penetrating into the lumen and involving the serosa and extraintestinal tissues. I do not believe that there are many tumors that can present these symptoms over a period of two years. Certainly the location of the palpable mass in the abdomen is consistent with the location of this lesion somewhere in the jejunum. I should like to characterize the behavior of the tumor for two years by calling it a lymphosarcoma that probably showed, at an early stage, some intraluminal protrusion and caused the early symptoms of pain and vomiting and obstruction, possibly through the mechanism of repeated intussusception. It is only later in the patient's course that we have evidence that the tumor began to ulcerate. I believe that this tumor had grown outward, adhering to many coils of the small intestine, and had finally begun to present a mass that could be felt. I suspect that the lesion was much more extensive in the small bowel than the x-ray evidence indicated. The extensiveness of the tumor was due to the early presence of malnutrition, possible malabsorption of certain food stuffs and the early presence of a severe refractory anemia. Possibly, the serum protein of 6.8 gm. was caused by a lymphosarcoma, which occurs in some cases, but I do not want to stress the importance of any one laboratory finding of that sort. There were undoubtedly metastases to the mesenteric lymph nodes. I am not completely satisfied with the explanation of the anemia or of the hypotension, the yellow color eighteen months previously and the more recent history of a brownish color. My diagnosis is lymphosarcoma of the jejunum with regional intestinal involvement and ulceration of the mucosa.

A PHYSICIAN: How about the pancreas?

DR. JACOBSON: In view of the ulceration of the mucous membrane of the jejunum on x-ray examination it seems to me that the tumor probably arose from the small intestine rather than from extraintestinal structures.

CLINICAL DIAGNOSIS

Carcinoma of jejunum.

DR. JACOBSON'S DIAGNOSIS

Lymphosarcoma of jejunum.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of jejunum.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was operated on by Dr. Sweet. I am sorry that he is not here to describe his findings at first hand. A large tumor of the jejunum was found within 10 cm. of the ligament of Treitz. The tumor involved the wall of the bowel and the adjacent mesentery and had seeded itself on another loop of jejunum, which had become adherent to it. At operation it had evidently been extremely difficult to preserve the blood supply of the transverse colon, but it was possible to resect the two loops of intestine and the large mass in the mesentery.

The specimen in the laboratory was an ulcerated tumor of the jejunum on the mesenteric side that did not completely encircle the bowel. The major mass of tumor lay in the mesentery and was 6 to 7 cm. in diameter. On microscopical examination it turned out to be a well differentiated, slowly growing adenocarcinoma of the jejunum. Cancers of the small bowel are relatively rare, but they do occur from time to time.

DR. JACOBSON: How much of the jejunum was actually involved?

DR. MALLORY: A small amount of jejunum was directly involved by the tumor, but the kinks and the adhesions may have thrown a considerable portion more or less out of function.

CASE 33202

Presentation of Case

A seventy-eight-year-old widow entered the hospital from a home for the aged complaining of severe abdominal pain and vomiting.

She had been well until three days previously, when, after a normal meal, she began to have intense, cramping abdominal pain in the midepigastrium with vomiting. Following this attack she continued to have intermittent sharp cramping pains radiating across the midabdomen every two to five minutes. Occasionally, the pain was referred to the back but never to the shoulder or the interscapular region. She could take nothing by mouth without vomiting, the vomitus often consisting of greenish, foul-smelling material. There had been no bowel movements or passage of gas during the five days before admission. Two enemas, as well as a laxative, had been given without result. The patient's general health had been good until the abrupt onset of the illness. She had lost no weight, and the bowels had moved regularly without evidence of blood or tarry stools. Two months previously a similar episode of vomiting had lasted only a few hours and had been relieved by bicarbonate of soda.

The past history revealed that both femoral necks had been fractured in falls — the right eight years, and the left eight months previously. Both fractures had been successfully treated by nailing. There had been no abdominal operations or pregnancies.

Physical examination revealed a slightly obese woman in no acute distress. The skin was moderately dehydrated without evidence of cyanosis or jaundice. The lungs were clear. The heart was somewhat enlarged on percussion. No murmurs were heard. The abdomen was diffusely tender without spasm, distention or palpable masses. The liver and spleen were not palpable. Pelvic examination was negative.

The temperature was 99.5°F., the pulse 80, and the respirations 30. The blood pressure was 130 systolic, 90 diastolic.

A plain film of the abdomen showed several gas-filled and fluid-filled loops of what appeared to be small bowel. No gas was seen in the colon. X-ray films of the chest were normal.

Examination of the blood revealed a hemoglobin of 16.5 gm. and a white-cell count of 12,500, with 60 per cent neutrophils. The urine showed a specific gravity of 1.012, a +++ test for albumin and no sugar or bile. The nonprotein nitrogen was 28 mg., the protein 8.0 gm., and the fasting blood sugar 149 mg. per 100 cc., and the chloride was 98 milliequiv. per liter. The serum amylase was 14 units. The van den Bergh reaction was 0.7 mg. per 100 cc. direct and 1.0 mg. indirect.

A Miller–Abbott tube was introduced, and intravenous fluids with dextrose and Amigen were administered daily. The patient continued to have occasional bouts of cramping abdominal pain. On the third hospital day a prophylactic bilateral femoral-vein interruption was done. The progress of the Miller–Abbott tube was followed by daily x-ray study. The tube progressed slowly through the proximal small bowel, several loops of dilated small bowel being noted distal to the advancing tip. By the seventh hospital day the tube had reached the distal ileum. At that time a single loop of dilated small bowel was seen on the left in the midabdomen. A barium enema done on this day showed a good flow, without hesitation, to the cecum through a spastic colon. Numerous diverticulums were noted throughout the colon. The terminal ileum was not seen. Several linear shadows were found in the right upper quadrant and were thought to outline the biliary tree. An overexposed film taken to clarify the situation in this area showed gas outlining the stomach and the duodenal cap. Overlying the latter shadow were several irregular linear collections of opaque material whose location was uncertain but was thought to be in the biliary tree. There appeared to be gas in a thin, branching channel extending upward from the location of the duodenal cap.

During the second week of hospitalization there were periods of freedom from pain. The patient passed several stools, consisting mostly of barium, and occasionally passed some gas. She remained essentially unchanged, however, with recurring pain, slight distention and some hyperactive peristalsis.

On the nineteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Edward Hamlin, Jr.: May we see the x-ray films?

Dr. Stanley M. Wyman: The chest films are essentially those of a woman with a moderately large heart; there is nothing specific about the picture. This next film shows the dilated small intestine and the Miller–Abbott tube starting down through the stomach. In a later examination a branching pattern of what seem to be gas-filled tubes is outlined in the right upper quadrant overlying the shadow of the liver. At the same time linear collections of increased density, apparently barium, lie in the region of the duodenal cap. These are the diverticulums in the colon.

Dr. Hamlin: Was barium given by mouth at any time?

Dr. Wyman: I believe that she was given one small swallow of barium.

Dr. Hamlin: That is important because otherwise it would be difficult to determine how barium reached the small bowel.

Can you demonstrate the air-filled biliary tree?

DR. WYMAN: I think that it is best seen in this film. This looks like the common duct, with shadows representing branching hepatic radicles.

DR. HAMLIN: The problem is one of an elderly person who obviously had small-bowel obstruction, probably not entirely complete. I say that because at entry, after difficulty for five days, there was relatively less evidence of small-bowel dilatation than she had later when she was being treated more adequately. In the later stage gas passed through when the Miller–Abbott tube was down, so that obstruction was not complete all the time.

The causes of small-bowel obstruction are many. The fact that there had been no previous operations is important. The patient was slightly old to have had congenital bands or adhesions, although I suppose that either diagnosis is a possibility. There is nothing in the x-ray picture to lead one to believe that she had volvulus of any sort, nor does the history suggest it. The lead that is given in the protocol, concerning the outline of the biliary radicles, cannot be ignored for obvious reasons, and immediately one thinks of gallstone ileus. I am going to end up believing that she had that without any question.

It is of interest to discuss briefly the treatment of an elderly person with dehydration and intestinal obstruction. Several years ago Dr. McKittrick* effectively demonstrated that in a patient with intestinal obstruction who is seen within the first twenty-four hours and in whom operation is done at once, the mortality rate will approach zero. If the patient is seen after the first twenty-four hours the hazard of anoxemia of a section of bowel is probably less than that of operation with the dilated loops of bowel that would be present. The treatment of this patient followed Dr. McKittrick's teaching in that she was hydrated; a Miller–Abbott tube was passed and kept down until the bowel was considerably less dilated, and the operation presumably was a fairly easy one and far less hazardous for her than if it had been done in the earlier period. To carry out this type of preoperative treatment is extremely important. Why it required nineteen days, I do not know. I think that the service deserves considerable credit for keeping her in an electrolytic and fluid balance for that period.

Gallstone ileus is a relatively rare condition, consisting of a large gallstone that produces inflammatory adhesions between the gall bladder and the small bowel. Gradually, erosion takes place, and the gallstone passes into the small bowel. Because the caliber of the small bowel is smaller at the terminal ileum than elsewhere, the gallstone almost invariably sticks there and produces intestinal obstruction, which is what I believe this patient had.

*McKittrick, L. S., and Sarris, S. P. Acute mechanical obstruction of small bowel: its diagnosis and treatment. *New Eng. J. Med.* 222:611-622, 1940.

CLINICAL DIAGNOSIS

Gallstone ileus?
Band adhesion: obstruction secondary to old diverticulitis?

DR. HAMLIN'S DIAGNOSIS

Gallstone ileus.

ANATOMICAL DIAGNOSIS

Gallstone ileus.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Dr. Risley, will you describe the operative findings?

DR. THOMAS S. RISLEY: As Dr. Hamlin prophesied, at operation a gallstone was found, but not at the ileocecal valve. It was somewhere in the midileum. There was no necrosis of the bowel at the site of the stone, and there was no obvious reason why the stone should have stopped at that particular point. The stone was movable, and it was relatively simple to milk it upward to a point above, where the bowel was more normal in appearance. It was pushed back several feet above the point where the bowel was edematous and dilated and was removed. There were numerous adhesions in the right upper quadrant, but no stones were palpable. This region was not explored.

DR. MALLORY: Dr. Robbins, have you ever been able to demonstrate stones in the small bowel?

DR. LAURENCE L. ROBBINS: Occasionally, we have, but of course certain gallstones contain so little calcium that such a demonstration is often impossible. I believe that in this case a film of the stone following removal showed a few flecks of calcium, but we were never able to identify it on the ordinary films.

DR. MALLORY: A gallstone that produces obstruction in the small bowel must be large, and such stones consist chiefly of cholesterol and contain little calcium. One would not expect a high percentage of them to show roentgenologically.

As Dr. Hamlin pointed out, this kind of stone is too large to go through biliary passages of normal size. The chances are at least nine out of ten that there is a fistula between the gall bladder and the intestinal tract through which the stone passed. That was not demonstrated in this case because the patient was old and had had intestinal obstruction for a long period, so that extensive exploration was probably not considered to be justified.

DR. BENJAMIN CASTLEMAN: How often have you seen gallstone ileus with carcinoma?

DR. MALLORY: I do not remember having seen it.

DR. BERNARD M. JACOBSON: How large does the stone have to be?

DR. MALLORY: This one was 3 cm. in diameter.

DR. WALTER BAUER: We had one a few years ago that was found during a gastrointestinal series — a barium-filled, instead of an air-filled, biliary tract.

DR. FLETCHER H. COLBY: The delay of nineteen days is interesting. Why was operation delayed?

DR. RISLEY: The obstruction was quite incomplete, and it appeared at one time as if the obstruction would be spontaneously relieved. It was thought that if the patient had a gallstone she might pass it. She was in poor condition, and it was hoped that the exploration might not be necessary. She was given a trial with removal of the Miller–Abbott tube and had a normal bowel movement, and it looked briefly as if the obstruction had been relieved; shortly after removal of the tube, however, she became obstructed once more. The first obstruction required quite a time for sufficient decompression to make exploration easy, and the same situation was encountered with the second obstruction.

DR. MALLORY: It is of interest that a patient can have such severe disease of the biliary tract as this patient must have had with nothing in the past history to suggest such a condition. She had been in the hospital on two or three previous occasions, and at no time did she complain of symptoms referable to the biliary tract.

DR. BAUER: Is that unusual? The incidence of gallstones at autopsy is high, is it not?

DR. MALLORY: Yes; but not in association with ulcerative cholecystitis.

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STREPTOMYCIN

STREPTOMYCIN has been generally available to the medical profession of this country for several months, and by now, most physicians, particularly those who are privileged to treat or to follow the course of patients in hospitals, have had the opportunity of observing the use of streptomycin in occasional patients of their own or of their colleagues. A considerable literature dealing with this antibiotic has also accumulated, and many clinical reports have become available, particularly during the past year. Many additional reports of its use will undoubtedly continue to appear in the near future. A fairly thorough review of the available literature on this topic is presented in this issue and in the preceding issue of the *Journal*.

Streptomycin, as pointed out in this review, has not lived up to all that was expected of it when it first made its appearance. Perhaps the profession had been led to expect too much because of the brilliant results that had so recently been achieved with penicillin. It has, however, proved quite useful, and without doubt, many persons already owe their recovery from various serious infections to treatment with streptomycin. It has provided an effective cure for certain infections for which other available antibacterial agents have not proved successful and offers an alternative or additional agent in some infections that are only partially affected by sulfonamides, penicillin or specific immune serums. It is the first agent to receive careful and extensive study in the treatment of tuberculosis, with some promise of at least limited success.

The exact place that streptomycin will occupy in the treatment of infections, particularly tuberculosis, cannot be predicted at this time. Its greatest disadvantage has proved to be the great ease with which resistant strains become established during the course of treatment. This alone may eventually limit, if not entirely vitiate, its usefulness in tuberculosis and in other infections, particularly those whose courses tend to be subacute or chronic. Its toxicity, although not of a high order, is significant. This is particularly true of the otic complications, which seem to be caused by the antibiotic itself and not by any impurity and which may leave serious and possibly permanent damage. Moreover, the treatment is expensive by any standard, and is likely to remain so. This is bound to be an important deterrent to its widespread use, particularly in view of its other limitations.

These facts justify a sustained and intensive effort to discover new, more potent and more widely effective chemotherapeutic and antibiotic agents. The discovery of the chemical structures of penicillin and streptomycin and the recent advances in the knowledge of bacterial metabolism in relation to chemotherapy offer considerable hope for synthesis of such agents in the not too distant future. In the meantime, the best use should be made of the agents that are now available.

FULL UTILIZATION OF HOSPITAL FACILITIES

A LETTER dealing with certain aspects of hospitalization appears elsewhere in this issue of the *Journal*. The correspondent's points are well taken, and from a businessman's point of view, it certainly is a waste of time and of invested capital to have facilities such as the operating room and the x-ray and laboratory departments functioning only part time. That this results in a great waste of bed days so far as the total number of patients is concerned is unquestionable. On the other hand, if beds are filled at all times, it seems reasonable to assume that the revenue to most financially embarrassed hospitals would not be appreciably greater whether the occupant of the individual bed changed every seven days or every fourteen. Fees for specific services would increase, but this would probably be counterbalanced by the cost of the necessary additional personnel. There would, however, be a decrease in the unit overhead cost, which in institutions such as the large teaching hospitals might result in considerable saving.

Regardless of the financial considerations, in these difficult days it is essential that hospital facilities should be used for the greatest good for the greatest number; indeed, about a year ago the need of a "seven-day week" was commented on editorially in the *Journal*.* The fact is inescapable that if a patient is occupying a hospital bed unnecessarily long it is a waste; and it is suggested that all hospitals, whether privately endowed or financed by community, state or nation, should seriously consider a change from a method of operation that results in such an obvious loss of urgently needed facilities.

*Editorial. Inadequacies of medical care. IV. Those concerning its adjuncts. *New Eng. J. Med.* 234:613, 1946.

The telephone number of the Massachusetts Medical Society has been changed to KENmore 5162.

The *New England Journal of Medicine* will retain its old number (KENmore 2094).

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BOYLE — John F. Boyle, M.D., of Lowell, died April 25. He was in his seventy-sixth year.

Dr. Boyle received his degree from Harvard Medical School in 1903. He was a former president of the Middlesex North District Medical Society and was a member of the New England Obstetrical and Gynecological Society.

A sister survives.

CARSLEY — Sidney R. Carsley, M.D., of Palmer, died April 19. He was in his seventy-second year.

Dr. Carsley received his degree from University of Vermont College of Medicine in 1902. He was medical examiner for the Eastern Hampden District and was a member of the staffs of the Mary Lane Hospital, Ware, and the Springfield Hospital. He was a fellow of the American Medical Association.

His widow and a son survive.

CASWELL — Bertram H. Caswell, M.D., of Somerville, died April 14. He was in his seventy-second year.

Dr. Caswell received his degree from Tufts College Medical School in 1903. During World War I he served as a captain in the Army Medical Corps. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

His widow and a stepdaughter survive.

HUNT — William O. Hunt, M.D., of North Falmouth, died April 19. He was in his ninety-third year.

Dr. Hunt received his degree from Harvard Medical School in 1877. He was the last surviving founder of Newton Hospital. Until his retirement from active practice in 1940, he had practiced medicine in Newtonville for fifty-nine years.

A daughter, four sons (one of whom, Dr. Harold O. Hunt, is a resident of North Falmouth), thirteen grandchildren and five great-grandchildren survive.

RONEY — Hugh B. Roney, M.D., of Pittsfield, died January 8. He was in his sixty-first year.

Dr. Roney received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1909. He was a member of the staffs of the House of Mercy and Hillcrest hospitals, Pittsfield.

MISCELLANY

NEW MEDICAL DEAN AT BOSTON UNIVERSITY

Dr. James M. Faulkner, director of the First and Third Medical Services, Boston City Hospital, and professor of medicine at the Tufts College Medical School, has been appointed dean of Boston University School of Medicine. Dr. Faulkner will succeed Dr. Donald G. Anderson, who has resigned as of June 1, to accept a position as secretary of the Council on Medical Education and Hospitals of the American Medical Association in Chicago.

Dr. Faulkner, the son of the late Dr. Herbert K. Faulkner, of Keene, New Hampshire, graduated from Harvard College and Harvard Medical School, and received training at the Massachusetts General Hospital, Rockefeller Institute for Medical Research and Johns Hopkins Hospital. He was associated with the Harvard Medical School at Thorndike Memorial Laboratory of the Boston City Hospital for ten years, being in charge of the Electrocardiographic Laboratory. He later joined the staff of the Boston University School of Medicine and the Massachusetts Memorial Hospitals, where he was in charge of the cardiac clinics.

Dr. Faulkner served in the Navy during the war, being in charge of the medical service at an English base hospital that cared for patients evacuated from the Normandy beach head. He received a commendation from Admiral Stark for this work, and attained the rank of captain before his discharge.

PASSANO FOUNDATION AWARD

Selection of Dr. Selman A. Waksman, microbiologist at the New Jersey Agricultural Experiment Station, New Brunswick, New Jersey, as the 1947 recipient of the Passano Foundation Award has recently been announced by the Board of Directors of the Foundation. Established in 1943 by Williams & Wilkins Company, medical publishers, of Balti-

more, the Foundation proposes to encourage medical research, especially that which has clinical application, and has established the award as one of its activities. Dr. Waksman receives the award for his original research in the field of antibiotics culminating with his discovery of streptomycin, which among its many uses gives promise of being of value in the successful treatment of tuberculosis.

Presentation of the $5000 cash award will be made at a dinner to be attended by about a hundred outstanding medical men at the Ritz-Carlton Hotel, Atlantic City, on Thursday evening, June 12, during the week of the centennial meeting of the American Medical Association. Sir Howard Florey, of Oxford, England, who was knighted for his development of the clinical applications of penicillin, will make a brief address, following which the award will be presented to Dr. Waksman. Dr. Waksman's address will be entitled "Antibiotics and Tuberculosis — a Microbiological Approach."

NOTE

Dr. Robert P. Knight, at present chief-of-staff of the Menninger Clinic, Topeka, Kansas, has recently been appointed medical director of the Austen Riggs Foundation, Stockbridge, Massachusetts. Dr. Edgerton McC. Howard, who is now serving as acting medical director, will become associate medical director. Dr. Knight will assume his new duties on September 1.

CORRESPONDENCE

"THE LOST WEEK-END"

To the Editor: Hospitals today are badly overcrowded and have long waiting lists. Emergency surgical patients are readily admitted in most instances; a spare room or bed is usually reserved for just such a contingency or a temporary arrangement is made, such as placing the patient, even though of private status, in a ward. A medical emergency fares less satisfactorily, and patients who present no emergency but who are ailing and require the facilities of a hospital for diagnosis are placed on the waiting list and have a poor chance of being admitted for weeks or months.

The chief reasons for crowded hospitals appear to be the following: (1) The Blue Cross, the Blue Shield and other types of hospital and medical insurance, which permit benefits if the patient is hospitalized; (2) the widespread use of penicillin, which, to be given effectively, usually requires hospitalization; (3) the scarcity of trained nurses for home duty; (4) the shortage in the hospitals of nursing personnel and technicians; (5) the increased cost of operating hospitals in such a way that they function properly; and (6) the common custom of hospitals to run at low speed during week ends and holidays. The last reason is, in my opinion, an extremely important one. At such times the nursing and technical departments are manned by skeleton crews, which attempt to function only on an emergency basis. Out-patient departments are closed, although there is no doubt that if they were open not only would many be helped who would otherwise hesitate to seek help because of the fear of losing a day's work and pay but also advice would be given to others that might later forestall serious illness for which hospitalization and abstinence from work would become imperative.

As a direct result of the above factors patients are obliged to remain in the hospital, often at great expense to themselves or to industry, to wait their turn for the various special examinations ordered by the physician. A patient who enters the hospital Friday afternoon and who pays $7 a day on the ward or $10 or more a day for a private room, does not relish the knowledge that only emergency work will be done for him until Monday and that even some of the work that has to be done may not be reported till Tuesday.

Faced with this unprecedented demand for admissions, what steps have the hospitals taken? They have appealed for more nurses to keep their wards open, and they have raised salaries. It seems to me the one step not taken to increase their usefulness is to eliminate the week-end or holiday vacation. Were this latter step taken, an extra one and a half days would become available weekly for routine hospital diagnostic procedures. Thus, approximately a week would be gained monthly, or seventy-five days yearly, which, added to about eight days for holidays, would amount to nearly three months each year. In this manner, the capacity of the hospital, in so far as routine diagnostic procedures are concerned, would be increased by about a third.

How can the hospital provide for the full-time use of facilities? Obviously, it will be necessary to increase the personnel and to stagger the working hours. A further raise in salaries may be required. To provide for additional medical personnel, it might be possible to arrange for so-called "floaters." Thus, a private roentgenologist might be induced to "spell" his resident brother for a week end or for a specific number of hours each week. The same would be true of the pathologist, anesthetist and so forth. This problem would not differ materially from that of arranging for the summer vacation or for prolonged illness.

The money necessary to run the hospital on this full-time schedule would become available from the increased income obtained by the more rapid turnover of patients. In addition, as the improved facilities and service offered by the hospital impressed the community, there would be a greater eagerness to contribute to its support.

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PROFESSIONAL RESPONSIBILITY

To the Editor: In reference to Dr. Stratton's statement in the March 20 issue of the *Journal* regarding my recent experience with the Court, I wish to present to the fellows of the Massachusetts Medical Society the facts of the case.

On the morning of February 16, at about 2:00 a.m., I was called to see a young woman who had been criminally attacked. The car in which she and her escort were riding had been stopped by blocking the road, the door window smashed, her escort ordered out by two masked men at gun point, the girl taken out by a third man at gun point and then criminally attacked by the three men in turn.

I was fully satisfied that the girl's story was true, and examination showed unmistakable evidence of assault. Her family made it plain that they wished nothing said of the matter and refused to consult the police. I agreed that it was a private matter and that, so far as I was concerned, their wishes would be respected.

On my return home, however, and on reflection of the incident, I decided that, for the protection of the public, the police should be notified of the affair. That same morning I gave all the details, excepting names, to the police and informed them that I was doing this without the patient's knowledge and against the expressed wish of her family.

Two weeks later, a young man was killed when two gunmen ordered him and his girl companion into the back seat of his car and took possession of the machine. The police then asked me for the identity of the young lady whom I had treated, on the supposition that this murder might have been committed by the same men who had assaulted her.

When permission was sought from the family for police questioning, they took the attitude that I had broken faith with them by reporting the incident. I told them that I had done so for the protection of the public and reminded them that I had not revealed the girl's identity and would not do so without their permission. They steadfastly refused to give the consent requested.

On my refusal to reveal the identity of the girl to the Grand Jury on professional grounds, I was jailed. The girl's family then came forward and arranged with the State Police for the questioning of the girl and her escort to effect my release.

I believe that it is unfortunate that, under existing Massachusetts statutes, a physician has only the Oath of Hippocrates as justification for keeping a pledge of privacy given to a victimized patient. I respectfully ask that the Committee on Legislation consider the desirability of effecting an amendment of the present law to grant to physicians the privilege that the public assumes we already possess and that is recognized by law in New York, Pennsylvania and many other states.

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Lowell, Massachusetts

TREATMENT OF HERPES ZOSTER WITH SULFADIAZINE

To the Editor: I have seen no mention in the literature of the use of the sulfonamides in the treatment of herpes zoster. Probably the reason for not using one of them is the general belief that herpes zoster is due to a virus, and it is well known that these drugs have no effect on virus diseases. The assumption that the disease is due to a virus may be wrong. Indeed, it may turn out to be of streptococcal origin, and one bit of evidence for this is its quick response to sulfadiazine.

In the last five years I have treated eight cases of herpes zoster with sulfadiazine, the usual dosage being 1 gm. every three hours for twelve or fifteen doses. In all but one of these cases, pain and discomfort did not persist more than a few days. Inside of forty-eight hours the rash began to fade, turning from red to reddish brown, with disappearance of the vesicles, and in the course of a few weeks it disappeared altogether. All but one of these cases were seen early in the disease, when there were comparatively few vesicles, which may account for their rapid response to treatment.

These cases are in marked contrast to a patient whom I treated before the sulfonamides were known. In this case the eruption extended in the course of a few days from the spinal column to the sternum, covering the right, lower thoracic region. It was a solid, bright red mass of papules and vesicles, about 7.5 cm. in width. The discomfort and pain were severe, requiring repeated doses of codeine and aspirin to control it. The patient was confined to her bed for nearly a month, with an elevation of temperature for the first two weeks. For six months after the rash subsided she complained bitterly of sharp, shooting pains in the right thoracic region, and even a year after the onset she still had occasional pain.

Since I have used sulfadiazine in these cases, I have seen nothing remotely resembling the severity of this case. After the rash has subsided, there have been no complaints or soreness in the area involved. In only one of the eight cases did the patient complain of pain after one week, and in this case, treatment was not begun until the rash was fully developed.

Most textbooks state that herpes zoster treated by orthodox methods ordinarily lasts from two to three weeks. My experience, prior to the use of sulfadiazine, leads me to believe that that prognosis is entirely too optimistic. The rash may fade or disappear in two or three weeks, but the pain, which is the chief factor, may persist for weeks, months and even years. In my experience, herpes zoster treated by orthodox methods is a prolonged, painful malady with an extremely uncertain prognosis.

NEIL C. STEVENS

Walpole, New Hampshire

AN IMPROVED GASTROSCOPE

To the Editor: In spite of the well established usefulness of gastroscopy with the flexible gastroscope, there are still blind areas in the stomach that are relatively inaccessible. These have been partly overcome by the development in England of the Hermon Taylor flexible gastroscope, on the handle of which there is a rachet that permits movement of the flexible portion after introduction into the stomach. This permits a much better view of the lesser curvature and posterior wall in the upper part of the body of the stomach. It also enables some increased visibility in the antrum. The slightly larger caliber of this instrument, making it a little more difficult to pass, is far outweighed by the better view obtained. In an occasional difficult case, one may have to revert to the original more flexible type of gastroscope.

I am now using the Hermon Taylor flexible gastroscope in every case, believing that the greatest advantages are, as claimed by the author, "abolition of blind areas in the stomach and the ability to move the objective about inside the stomach so as to inspect any particular area closely at will and to do so at more than one angle." The instrument is manufactured by the Genito-Urinary Manufacturing Company, Limited, 28a Devonshire Street, London W.1, England. After paying the U. S. Customs duty, the cost is approximately the same as that of American-made gastroscopes.

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BOOK REVIEWS

Medicine in Industry. By Bernhard J. Stern, Ph.D. 8°, cloth, 209 pp. New York: The Commonwealth Fund, 1946. $1.50. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order.

In this monograph Dr. Stern discusses the social, economic, legal and professional aspects of industrial medicine. Data are presented on the rates of industrial disability and the limited extent of preventive services. He deals with recent developments in health and insurance programs, the problems of the handicapped and the relations between the industrial physician and the general practitioner. The work is well documented, with statistical tables and adequate lists of references to the various topics.

The first chapter is devoted to a well written short history of the subject dating from ancient times to the present. Then follow in order chapters on social and legislative backgrounds, the extent of industrial disability, the handicapped worker, preventive services, medical care and health insurance and the industrial physician. An appendix consists of a table showing industrial prepayment medical plans in operation in various industries in the United States and giving essential information concerning the plans. The book is well published and should be in all medical and public, as well as industrial, libraries and should prove valuable to all persons interested in the subject.

Eight Years of Public Health Work: Jones County, Mississippi, 1937–1944. By Harry E. Handley, M.D., and Carolina R. Randolph. 12°, paper, 80 pp., with 47 tables. New York: The Commonwealth Fund, 1946. 50 cents.

A continuous, well balanced program of county health work in Jones County, Mississippi, with emphasis on special problems, proved most effective during the period 1937–1944, during which almost $300,000 was spent on public-health work. The county has an area of 706 square miles, and the population was 49,227 at the time of the 1940 census. White persons comprised 72 per cent of the population, and 47 per cent were concentrated in two urban communities.

This report gives a detailed account of the work on sanitation, children under school age, school children and adults. The work on communicable diseases is emphasized. The Commonwealth Fund made substantial financial contributions to the basic budget of the health department in an effort to demonstrate that an adequate health service is worth while and deserving of local tax support. The local, state and federal governments also contributed to the budget. The Commonwealth Fund is currently making contributions for new services in maternity care and immunization against whooping cough. The report contains a wealth of well organized and documented information.

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Moses J. Stone, M.D., and Paul Dufault, M.D. With a foreword by Henry D. Chadwick, M.D. 12°, cloth, 325 pp., with 93 illustrations. Philadelphia: Lea and Febiger, 1946. $3.50.

Although this manual is a continuation of the previous editions by John B. Hawes and Moses J. Stone, it is practically a new book, since it has been almost entirely rewritten. The work is designed for medical students and general practitioners. The material is presented in a concise, well organized manner and is comprehensive in its scope. Emphasis is placed on radiologic diagnosis. Tracheobronchial tuberculosis and its operative treatment and artificial pneumothorax and thoracic surgery as means of treatment are discussed in special chapters. The text concludes with two chapters on tuberculosis in industry and on the social aspects of the disease. The first chapter is a short historical sketch of tuberculosis from 1500 B.C. to the present time. Reading lists are appended to each chapter. The volume is well published and should prove valuable to all physicians interested in the disease.

Human Embryology. By Bradley M. Patten, M.A., Ph.D. 8°, cloth, 776 pp., with 446 illustrations. Philadelphia: Blakiston Company, 1946. $7.00.

Embryology has within recent decades gone through a tremendous activity, especially in the field of its morphology — a morphology, it is true, that is not static but changing. The

subject has been handled mainly as a series of superimposed changes of architecture. One may say with reasonable certainty that it is now reasonably complete — just as gross morphology was quite definitely established seventy-five or ninety years ago.

For many years Dr. Patten has contributed heavily to the development of this science, and he is admirably suited, both by his knowledge and his genius for exposition, to writing this volume, which stands as an excellent and quite complete codification of the morphology of embryology.

It is well to have available such a well crystallized and understandable text of this aspect of embryology, for one may dare to assert that we stand on the threshold of a more comprehensive science of the embryo — a science in which successful attempts have already been made in physiology, chemistry and pathology.

A few examples may be chosen from divergent fields: the experiments in embryo mechanics, including the potency of isolated anlage and the presence of "organizers" of "energizers" developed in the writings of Spemann, Waddington and Weiss; the influence of the sexual hormones on both sexual and other development — for example, that of estrogen on bone growth (Bremer); the influence of transmitted defects of the glands of internal secretion on body build (Stockard); and the time of assumption of function by the various organs, such as the prenatal and postnatal maturation of the various paths of the nervous system (Conel).

A few problems of embryonic pathology have been explained: the transmission of congenital defects from "tainted" stock, the cause and prevention of erythroblastosis fetalis and the causation of congenital defects by rubella in the mother.

The aim of the comprehensive embryology of the future appears to be to make embryology now and in later times no longer merely a preclinical science but one of daily clinical application. It is necessary for the intelligent physician to familiarize himself with embryology. For him, as well as for the medical student, this work may be heartily recommended. It is authoritative and written lucidly and with much emphasis on application. The format is likewise excellent, with many fine drawings.

Group Psychotherapy: Theory and practice. By J. W. Klapman, M.D. 8°, cloth, 344 pp., with 14 illustrations. New York: Grune and Stratton, 1946. $4.00.

The expression "so many and so few" can well be applied to the present situation regarding the mentally ill and the number of psychiatrists available. Group psychotherapy arose out of dire necessity and is still in the formative stage. This book is of value not only to sum up past and present knowledge in the field but also to point the way for the formulation of technics.

After a brief account of the development of group psychotherapy, the author traces its mental, moral and cultural origins. The developmental defects due to social isolation are emphasized, and the unique value of the demonstration of social standards and social conscience in group psychotherapy is indicated.

Methods used vary from the analytic school to the repressive, inspirational modes of psychotherapy. The personality of the therapist is of great importance. The action of numerous intragroup factors is described. Whenever possible, the procedure should be used in conjunction with individual psychotherapy.

Group psychotherapy is viewed as a method of affective re-education — "an adjustment of internal relations to external relations." For this purpose the lecture method and class and discussion periods are valuable. The psychodrama is used to "bring the patient to maturity by easy and gradual stages."

Other fields for group psychotherapy are in the outpatient clinic, for the treatment of problem children and their mothers and in private psychiatric practice.

Ancillaries to group psychotherapy are encouragement of hobbies and special interests, clubs, special radio programs, institutional publications and a public-relations program for mental hospitals.

The results are difficult to estimate. By means of a number of objective tests and evaluation by therapist and patient, they appear gratifying. Education by any method is a long-term project.

Oral Medicine. By Lester W. Burket, M.D., D.D.S. With a section "Oral Aspects of Aviation Medicine," by Major Alvin Goldhush, D.C., A.U.S. 8°, cloth, 674 pp., with 350 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $12.00.

In this volume the objective of correlating many of the diseases of the oral cavity with systemic disease has been successfully reached. The author, who is a physician and dentist studying oral disease in a well organized clinic, is especially fitted to evaluate and stress the diagnosis and treatment of the important and frequent diseases of the oral cavity.

Case records of the patient with oral disease should include a detailed history, with a description of the lesions and all the pertinent laboratory procedures that are used in the diagnosis of any pathologic process in the body. This the author has accomplished by a complete type of record used in the department of oral medicine.

Ten sections, which include all aspects of diseases of the oral cavity, as well as a regional diagnostic index, give a complete coverage of oral disease. Ten color plates with sixty subjects are especially useful in depicting some of the more frequent diseases of the tongue and buccal mucosa.

One criticism of the volume is the tendency to include discussions on many local and systemic diseases that are unrelated to oral disease. Reference to books on general medicine would serve as more practical guides to the dentist or dental student in rounding out his knowledge of the relation of constitutional and oral disease.

The book can be recommended as a textbook in oral medicine for the dental student and as a guide to the practicing dentist and physician in correlating lesions of the oral cavity and disease found elsewhere in the body.

Western Reserve University Centennial History of the School of Medicine. By Frederick C. Waite, A.M., Ph.D. 8°, cloth, 588 pp., with 15 illustrations and frontispiece. Cleveland: Western Reserve University Press, 1946. $6.00.

This centennial volume records, after the pattern of the Chinese drama, the history of the School of Medicine of Western Reserve University as a series of episodes in a progressive educational institution in which the professors are the chief actors and the students are the audience. In so doing, it epitomizes the history of medical education prior to the foundation of Western Reserve in 1843. An account is also given of the three rival local medical colleges, of homeopathic medical education in Cleveland and of several local hospitals. The work thus becomes a history of all institutional medical education in Cleveland during its first hundred years. The volume is divided into five books — a prologue, "The First Half-Century," "Ancillary Events," "The Second Half-Century" and biographical material constituting an epilogue.

The author, well known as a medical historian for his work on Vermont Medical College was a teacher at Western Reserve for over fifty years, having been appointed professor of histology and embryology in 1901. His volume, which is exceptionally well written and entertaining, is a valuable and scholarly contribution to the history of medical education in America.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Sex Education: A Guide for parents, teachers and youth leaders. By Cyril Bibby, M.A., M.Sc., F.L.S., education officer to the Central Council for Health Education, England. 8°, cloth, 311 pp. New York: Emerson Books, Incorporated, 1946. $2.50.

This English book has been revised by the changing of words and phrases having different meanings in the United States and by the deletion of passages not of interest to American readers. Footnotes have been added explaining British conditions. The subject is discussed from the viewpoints of

the parent and the school. In the long chapter entitled "In Search of Knowledge" various types of questions propounded by children are noted, and a pattern for answers is suggested by the author. The final chapter discusses the opposition to sex education and the need for such education. In the appendixes will be found a tentative scheme for education, specimen circulars to be sent to parents and specimen lectures on the subject. For reference purposes the absence of an index is to be deplored. This text should prove useful to all interested persons.

Medical Uses of Soap: A symposium. Edited by Morris Fishbein, M.D. 8°, cloth, 195 pp. Philadelphia: J. B. Lippincott Company, 1946. $3.00.

This second printing of a valuable monograph first published in 1945 has an additional chapter on the surgical uses of soap.

Endocrine Function of the Hypophysis. By Harry B. Friedgood, M.D., assistant clinical professor of medicine, University of Southern California School of Medicine, and senior attending physician, Los Angeles County Hospital. 8°, cloth, 211 pp., with 36 illustrations. New York: Oxford University Press, 1946. $4.50. Reprinted from *Oxford Loose-Leaf Medicine.*

By reprinting this monograph the Oxford University Press makes it possible for interested physicians and small libraries to own this concise but comprehensive treatise without having to procure the complete *Oxford Medicine.* The work is divided into five parts. The first discusses anatomy, embryology and phylogeny of the hypophysis, the second, the cytophysiology and biochemistry of the adenohypophysis, the third, the biologic, biochemical, physiologic and genetic concepts of growth, the fourth, the chemical disorders of growth and the fifth, the cytophysiology, biochemistry and pharmacology of the neurohypophysis. This monograph should be in all medical libraries and in the collections of all persons interested in the subject.

Principles of Hematology, with 106 Illustrative Cases. By Russell L. Haden, M.D., chief, Medical Division, Cleveland Clinic. Third edition, revised. 8°, cloth, 366 pp., with 173 original photomicrographs and 95 original charts and drawings. Philadelphia: Lea and Febiger, 1946. $5.00.

This manual is written for the student and physician and not for the specialist, and emphasis is therefore placed on the fundamental principles of hematology. Highly technical procedures, such as the study of the Rh factor, are omitted. The type has been completely reset, and corrections have been made to bring the subject up to date, including a description of the technic of bone-marrow puncture and the study of bone-marrow films. The book is well printed on good paper with a good type and is well illustrated.

White House Physician. By Vice-Admiral Ross T. McIntire, surgeon general of the Navy. 8°, cloth, 244 pp., New York: G. P. Putnam's Sons, 1946.

Dr. McIntire was the personal physician of President Roosevelt from the day of his first inauguration in 1933 until his death on April 12, 1945, and was also his companion, friend and confidant. He accompanied the President on his many journeys — to Newfoundland, where the Atlantic Charter was signed off the coast, Casablanca, Teheran, Yalta and Egypt.

He speaks with authority on the health and physical fitness of the President and of his struggle to overcome his infirmity due to infantile paralysis. He tells of the reasons behind his running for the presidency in 1940 and 1944. The volume is also an inside story of the political life of the presidential years. The text is written in an easy narrative style.

Courage and Devotion beyond the Call of Duty: Being a partial record of official citations to medical officers in the United States armed forces during World War II. Second preliminary edition, July, 1946. 12°, paper, 1024 pp. Evansville, Indiana: Mead Johnson and Company, 1946. Free.

The first issue (November, 1944) contained only 256 pages. The present text is divided into two parts, citations to individuals and citations to groups. Information is incomplete on a number of physicians and a few groups listed at the end of the volume, and the publisher invites corrections and additions and further information prior to issuing the final de luxe edition. This book is a valuable biographical reference source.

Manual of Applied Nutrition. A publication of the Dietary Department, Johns Hopkins Hospital. Second edition. 8°, paper, 103 pp. Baltimore: Johns Hopkins Hospital, 1946. $1.50.

This manual has been revised and edited by a group representing several clinical departments and the Nutrition Committee of the Johns Hopkins Hospital. All available knowledge and experience have been used in its preparation, and although compiled for the use of a particular hospital, it should prove useful to clinicians and dietitians everywhere. It contains a wealth of material on all types of diets, general and special, given in terms of food constituents, as well as routines for special hospital services. There is a section on the feeding of infants and children. Other special material includes recommended normal dietary allowances for men, women and children, tables of normal measurements of males and females from birth to twenty years in relation to age and height, physiologic data concerning biologic body substances, food values of common substances, data for acid-base calculations, routine house diets and high-calorie diets. This text should prove valuable to medical librarians as a reference source.

Health Examinations. Prepared for the Medical Society of the County of New York by the Special Committee on Preventive Medicine. 8°, paper, 144 pp. Reprinted by Mead Johnson and Company, 1946. Free.

In this short manual a number of physicians discuss briefly the various topics relating to health examinations in young and old persons, from the newborn infant to persons over sixty-five years of age. Included are chapters on premarital and prenatal examinations, the emotional development of children from birth to the sixth year and from the sixth to the twelfth year, the psychology of adolescence and the emotional factors in senescence. Emphasis is placed on the healthy adult, especially between forty-five and sixty-five years of age. Special chapters are devoted to the ears, eyes, teeth and nutritional deficiency diseases. These outlines should prove useful to all physicians called on to make periodic health examinations.

A Memoir to the Academy of Sciences at Paris on a New Use of Sulphuric Ether. By W. T. G. Morton, of Boston in the U. S. A. Presented by M. Arago in the autumn of 1847. With a foreword by John F. Fulton, M.D. $1.50. Historical Library, Yale Medical Library, Publication No. 14. 8°, paper, 24 pp. New York: Henry Schuman, 1946.

In this memoir, written by Morton in his twenty-eighth year, he gives the background of his discovery and the relations of his claims to those of Wells and Jackson. The appendix printed with the original French edition, but not reprinted in Littell's *Living Age,* is omitted in this reprint. The original memoir is rare, and this inexpensive edition should be welcomed by all persons interested in medical history and should be in all medical-history collections.

Notes on Nursing: What it is, and what it is not. By Florence Nightingale (London, 1859). 8°, cloth, 79 pp. Reprinted. Philadelphia: J. B. Lippincott Company, 1946. $1.25.

This reprint is an exact offset facsimile of the original printing of a classic in the field of nursing. It includes even the advertisements appended to the text. It is recommended for all libraries, medical, nursing and public, and this inexpensive edition makes the volume available to all nurses and others interested in the history of nursing.

Psychotherapy in General Medicine. By Geddes Smith, associate, The Commonwealth Fund. 8°, paper, 38 pp. New York: The Commonwealth Fund, 1946. 25 cents.

This pamphlet gives a detailed report of a postgraduate course in psychotherapy conducted in April, 1946, at the Center of Continuation Study, University of Minnesota.

Twenty-five physicians attended the lectures and seminars for a period of two weeks. The course was given to ascertain whether the general practitioner could be educated at the postgraduate level to care for psychoneurotic patients encountered in his general practice. The immediate results were the recognition by both students and instructors of new possibilities in the general practice of medicine, a warm response by clinic patients to treatment and a conviction on the part of most of the students that their usefulness and morale as physicians had been strengthened.

Sir W. Arbuthnot Lane, C.B., M.S., F.R.C.S.: His life and work. By W. E. Tanner, M.S., F.R.C.S. 8°, cloth, 192 pp., one portrait. Baltimore: Williams and Wilkins Company, 1946. $4.50.

This life of an eminent British surgeon covers the whole of his professional career from his student days until he became surgeon to Guy's Hospital. The surgical achievements of a man notable for his work on fractures and abdominal surgery and his advocacy of colectomy are depicted by Mr. Tanner throughout the text. One chapter is devoted to a trip to America in 1918 as a member of a committee to stimulate interest in the cause of the Allies. A complete bibliography of Lane's published writings comprising three hundred and forty-six titles, arranged by subjects and compiled by Mr. G. A. R. Winston, Wills's Librarian of Guy's Hospital, is appended to the text. This biography is recommended for all medical-history collections.

Principles of Neurological Surgery. By Loyal Davis, M.D., Ph.D., D.Sc. (hon.), professor of surgery and chairman of the Division of Surgery, Northwestern University School, Chicago. Third edition, thoroughly revised. 8°, cloth, 540 pp., with 192 illustrations. Philadelphia: Lea and Febiger, 1946. $7.50.

This standard text, intended for the use of medical students and general practitioners, has been revised to include the knowledge gained by the author and others in World War II. The volume is well printed on good paper, and the material is well organized. The illustrations and plates are excellent. The book is recommended for all medical libraries.

Currents in Biochemical Research. Edited by David E. Green. 8°, cloth, 486 pp. New York: Interscience Publishers, 1946. $5.00.

This collection of essays covers the whole field of biochemistry and is the joint endeavor of thirty collaborators who are specialists in their particular fields. The work is semipopular in character and written in simple language but on a scientific plane and without sacrifice of scholarship. The contributions emphasize the focal position of biochemical research in biology, chemistry and medicine. They invade the fields of organic, analytical and physical chemistry and encompass pharmacology, chemotherapy, public health, genetics, photosynthesis and agriculture. The contrast between the type used and the soft paper is not good and makes for difficult reading. The volume is recommended for all medical libraries for reference purposes.

Modern Drug Encyclopedia and Therapeutic Index. Edited by Alexander B. Gutman, Ph.D., M.D., assistant professor of medicine, Columbia University, College of Physicians and Surgeons, attending physician, Presbyterian Hospital, and associate attending physician, Vanderbilt Clinic, New York City. Third edition. 8°, cloth, 1157 pp. New York: Yorke Publishing Company, Incorporated. $10.00.

This new edition of a standard reference work has been completely rewritten and reset. Obsolete preparations have been deleted, new drugs and biologicals have been added and the arrangement of the material has been simplified. It is planned to keep the volume up to date by the issuance of supplements from time to time in which new preparations will be described. Comprehensive indexes of therapeutic uses and drugs arranged by manufacturers and distributors add greatly to the value of the work. A good general index concludes the volume. The material is well arranged and divided into pharmaceuticals, biologicals and allergens. The text is well printed, and the type composition makes for easy use. The volume is recommended for all medical libraries and should prove valuable to physicians and others.

Clinical Laboratory Diagnosis. By Samuel A. Levinson, M.D., Ph.D., director of laboratories, Research and Educational Hospitals, Chicago, and professor of pathology, University of Illinois College of Medicine; and Robert P. MacFate, Ch.E., M.S., Ph.D., assistant director of laboratories, Research and Educational Hospitals, Chicago, and assistant professor of pathology, University of Illinois College of Medicine. Third edition, thoroughly revised. 8°, cloth, 971 pp., with 192 engravings and 15 plates. Philadelphia: Lea and Febiger, 1946. $10.00.

This standard treatise has been brought up to date, and a few new methods have been added. The chemical methods have been critically revised, and all other laboratory procedures have been changed to conform to the latest methods. A new chapter on tropical medicine and new material on penicillin in the blood, acid phosphatase, the latest bone-marrow findings with ten new pictures of bone-marrow films, Diodrast and inulin clearance tests, anthocyamin and phenylpyruvic acid in urine have been added. The text is well printed with a good type on heavy paper. The work is recommended for reference purposes.

NOTICES

MASSACHUSETTS PHYSICIANS' ART ASSOCIATION

The first yearly exhibition of works of art by members of the Massachusetts Physicians' Art Association will be held on the fourth floor, Hotel Statler, Boston, throughout the meeting of the Massachusetts Medical Society, May 20 to 22.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The annual meeting of the Massachusetts Medico-Legal Society will be held in Parlor C, Hotel Statler, Boston, on Wednesday, May 21, at 2:45 p.m.

PROGRAM

The District Attorney and the Medical Examiner. Hon. George E. Thompson, district attorney, Middlesex County.
Business meeting.
Refreshments.

All medical examiners, whether or not members of the Massachusetts Medico-Legal Society, are cordially invited to attend.

NEW ENGLAND HEART ASSOCIATION

The annual Henry Jackson Lecture, under the auspices of the New England Heart Association, will be given by Professor John McMichael, of the Postgraduate Medical School, London, England, at 8:15 p.m. on Monday, May 26, at the Boston Medical Library. His subject will be "Heart Failure."

A short business meeting will precede the lecture. Interested physicians and medical students are cordially invited to attend.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Sunday, June 1, through Saturday, June 7, 1947. The Hotel William Penn in Pittsburgh will be the headquarters for the Board. Formal notice of the exact time of each examination will be sent to candidates several weeks in advance of the examination dates. Hotel reservations may be made by direct application to the Hotel William Penn.

Candidates in Military or Naval Service are requested to keep the Secretary's office informed of any change in address.

Applications are now being received for the 1948 examinations. For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

(*Notices continued on page xix*)